1093 CLN-617 COMBINES IL-2 AND IL-12 IN A SINGLE MOLECULE TO OPTIMALLY BALANCE SAFETY AND EFFICACY UPON INTRATUMORAL INJECTION

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Background IL-2 and IL-12 synergistically mediate anti-tumor immunity but trigger severe adverse events. 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 intratumoral (IT) administration and retention via LAIR2-mediated collagen binding. Here, we investigate the mechanism of action of a murine CLN-617 surrogate (mCLN-617) and elucidate the benefits of co-delivery of IL-2 and IL-12 in a single molecule.

Methods *In vivo* studies were conducted with mCLN-617 (IL12-LAIR1-MSA-IL2) in B16F10 and MC38 syngeneic tumor models. Cytokines were measured by Mesoscale Discovery, and cells analyzed by flow cytometry and T cell receptor (TCR) sequencing from blood and tumor samples.

Results Following mCLN-617 treatment, complete responses with no significant body weight loss were observed in checkpoint-refractory tumor models, including B16F10, CT26, and MC38. In mice implanted with two MC38 tumors, 100% of mCLN-617-treated tumors and 40% of non-treated tumors were eradicated, demonstrating a robust abscopal effect. When combined with systemically delivered anti-PD1 antibody, 100% of non-treated tumors also showed a complete response. Efficacy of mCLN-617 in both the treated and non-treated tumors was partially dependent on CD4+ and CD8+ T cells, IFNγ, and BATF3+ dendritic cells (DCs). mCLN-617 treatment was associated with >5-fold increase in CD8:Treg ratio and significant expansion of DCs in both tumors, and expansion of tumor-associated T cell clonotypes in peripheral blood. A combination of IL-2 and IL-12 co-administered on separate molecules (LAIR1-MSA-IL2 and IL12-MSA-LAIR1) showed efficacy similar to mCLN-617 in B16F10 tumor-bearing mice with >90% tumor growth inhibition in the injected tumor. However, the combination of individual agents triggered >10% body weight loss while mCLN-617 led to no body weight loss, suggesting IL-2 and IL-12 were delivered more safely on a single molecule. IT injection of MC38 tumors with mCLN-617 triggered a 15-fold reduction in IFNγ production in serum compared to IL12-MSA-LAIR1, demonstrating a safety advantage of mCLN-617 and suggesting IL-12 in mCLN-617 was functionally de-tuned. Robust immune infiltrates in both treated and non-treated tumors were observed upon mCLN-617 treatment, compared with LAIR1-MSA-IL2 or LAIR1-MSA-IL2 alone.

Conclusions mCLN-617 drove a robust abscopal effect mediated by antigen presentation and systemic cellular immunity. Co-delivery of IL-2 and IL-12 in a single molecule optimally balanced safety and efficacy. CLN-617 is currently in Phase 1 dose escalation in patients with advanced solid tumors.

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