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Abstract CT269: First-in-human trial in patients with metastatic colorectal cancer using CRISPR-engineered tumor infiltrating lymphocytes in which the intracellular immune checkpoint *CISH* is inhibited FREE

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Abstract

Background:

Given the dramatic rise in incidence of colorectal cancer in young adults, there remain limited treatment options effective in metastatic disease. Although T cell-based therapies have been successful in treating highly antigenic cancers, like melanoma and lung, they have not yet been shown to induce consistent and durable tumor regression in common epithelial malignancies, including metastatic colorectal cancer (mCRC). CISH (Cytokine inducible SH2 containing protein) is a novel intracellular checkpoint target demonstrating PD-L1 ligand independent mechanisms of enhanced anti-cancer activity. Given that CISH is not currently tractable via antibody or small molecule drug modalities, we employed CRISPR for precise inhibition of *CISH* in tumor infiltrating lymphocytes (TILs). Here, we provide the first clinical report of safety and anti-tumor activity of *CISH* edited TILs in 12 patients with metastatic gastrointestinal cancers (NCT04426669), including a clinical complete response (CR) in a young-adult patient with immunotherapy-refractory mCRC.

Methods:

Tumors were surgically resected for TIL harvest, followed by a rapid expansion protocol and CRISPR/Cas9 knockout (KO) *CISH*. CISH KO, neoantigen-reactive TILs were expanded, then infused following non-myeloablative lymphocyte depleting (LD) chemotherapy

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(cyclophosphamide & fludarabine) followed by high-dose IL-2. To establish mechanistic attribution of the CR, we used iR-RepSeq+ for serial analysis of the TCR immune repertoire.

Results:

Our CRISPR engineering led to KO of *CISH* in T cells with high-efficiency (>90%) without detectable off-target editing. We safely dosed patients at all five dose levels (range: 1.91e ^{8} to 9.93e^{10} cells). No dose-limiting toxicities attributable to the *CISH*-KO TIL product were observed. Adverse events were consistent with established risks of LD chemotherapy, IL-2, or disease progression. A durable ongoing complete response (>21 months) was achieved in a patient with microsatellite instability-high (MSI-H) mCRC refractory to anti-PD1/CTLA-4 combination therapy.

Conclusions:

We provide the first clinical report of CISH checkpoint targeting via genetically modified T cell therapy, with complete response in a patient with mCRC. Persistence and expansion of unique TCR clonotypes detected in neoantigen responsive TIL was temporally consistent with spikes in *CISH* edited alleles detected by NGS assay; in the patient with CR, four of the clonotypes exhibiting prolonged persistence greater than one-year post-infusion exhibited significantly reduced or undetectable expression of *CISH* compared to the total infused TIL population. Given these findings, further investigation of CISH checkpoint inhibition, via gene and cell therapy, and next-generation small molecule drugging modalities, is underway.

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