A PHASE I STUDY OF PERSONALIZED ADOPTIVE TCR T CELL THERAPY IN PATIENTS WITH SOLID TUMORS: SAFETY, EFFICACY, AND T CELL TRAFFICKING TO TUMORS OF NON-VIRALLY GENE EDITED T CELLS

Background NeoTCR-P1 is a personalized autologous T cell therapy for treatment of patients with solid tumors. Neoantigen-specific T cell receptors (neoTCRs) were isolated from the patients’ own circulating CD8 T cells using the imPACT Isolation Technology®, followed by non-viral precision genome engineering into an autologous apheresis product for infusion back into the patient.

Methods This phase 1 trial is a first-in-human, multi-center, dose-escalation study to evaluate the safety, tolerability, and manufacturing feasibility of NeoTCR-P1 alone or in combination with IL-2 in solid tumors.

Patients with TCRs identified at screening and meeting eligibility criteria underwent apheresis to manufacture personalized NeoTCR-P1 cell product. Lymphodepleted patients received a single dose of up-to-three distinct NeoTCR cell products, and T cell persistence and trafficking to a variety of solid tumors.

Results Sixteen patients were infused with NeoTCR-P1 T cells including patients with MSS-colorectal cancer (11), breast cancer (2), ovarian cancer (1), melanoma (1), or non-small cell lung cancer (1). Four of the sixteen patients were treated with NeoTCR-P1 + IL-2.

Two patients experienced toxicities associated with NeoTCR-P1 cell infusions: a grade 1 CRS and a grade 2 ICANS. Five patients had stable disease as their best response at their first tumor assessment (day 28).

NeoTCR+ T cells detected in the peripheral blood had an average peak of 3.6% (range 0.9-7.3%) for DL1, 11.7% (7.7-20.8%) for DL2, and 19.8% (12.0-37.3%) for DL3. Increases in NeoTCR T cells were observed at higher dose levels, stronger lymphodepletion, or higher gene editing rates of the infused product.

Eight post-infusion biopsies were available for sequencing and imaging analysis; 17 of 22 neoTCR-T cells were detected in post-infusion biopsies with 12 neoTCR-T cells among the top 4% of CDR3 sequences detected. The targeted neoantigens were detected in 7 of 8 post-treatment biopsies (15 of 22 targets), and personalized ctDNA confirmed targeting of a predicted sub-clonal mutation. An APOBEC signature and HLA-LOH were identified as potential mechanisms of resistance. By single-cell, spatial molecular imaging, neoTCR-T cells were visualized in post-treatment biopsies and found to differentially express potential markers of engagement.

Conclusions This study demonstrates the feasibility of isolating and manufacturing NeoTCR-T cells using non-viral precision genome engineering, the safety of infusing up-to-three gene edited NeoTCR-T cell products, and T cell persistence and trafficking to a variety of solid tumors.

Trial Registration NCT03970382

Ethics Approval Ethics approvals have been obtained from each clinical site enrolling patients: City of Hope, Duarte, California; University of California Los Angeles, Los Angeles California; University of California, Irvine Medical Center, Orange, California; University of California, Davis, Sacramento California; University of California, San Francisco, San Francisco California; Northwestern University Medical Center, Chicago Illinois; Memorial Sloan Kettering Cancer Center, New York, New York; Tennessee Oncology, Nashville, Tennessee; and Fred Hutchinson Cancer Research Center, Seattle, Washington.


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