1478 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

[1]Susan Foy, [1]Kyle Jacoby, [2]Daniela Bota, [1]Theresa Hunter, [3]Adam Schoenfeld, [1]Zheng Pan, [1]Eric Stawiski, [1]Yan Ma, [1]William Lu, [1]Songming Peng, [1]Clifford Wang, [1]Benjamin Yuen, [1]Olivier Dalmas, [1]Katharine Heeringa, [1]Barbara Sennino, [1]Andy Conroy, [1]Michael Bethune, [1]Ines Mende, [1]William White, [1]Monica Kukreja, [1]Swetha Gunturu, [1]Emily Humphrey, [1]Adeel Hussaini, [1]Duo An, [1]Boi Quach, [4]Alphonsus Ng, [4]Yue Lu, [1]Chad Smith, [5]Katie Campbell, [1]Daniel Anaya, [1]Lindsey Skrdlant, [1]Eva Huang, [1]Ventura Mendoza, [1]Jyoti Mathur, [1]Luke Dengler, [1]Bhamini Purandare, [1]Robert Moot, [1]Michael Yi, [1]Roel Funke, [1]Alison Sibley, [1]Todd Stallings-Schmitt, [6]David Oh, [5]Bartosz Chmielowski, [7]Mehrdad Abedi, [8]Yuan Yuan, [9]Jeff Sosman, [10]Sylvia Lee, [11]Claire Williams, [11]Sean Kim, [11]Matthwe Keefe, [11]Michael Leon, [11]Youngmi Kim, [11]Jason Reeves, [11]Wes Goldman, [12]David Baltimore, [4]James Heath, [1]Alex Franzusoff, [5]Antoni Ribas, [1]Arati Rao*, [1]Stefanie Mandl. *[1]PACT Pharma, South San Francisco, CA, United States; [2]University of California, Irvine, Orange, CA, United States; [3]Memorial Sloan Kettering Cancer Center, New York, NY, United States; [4]Institute for Systems Biology, Seattle, WA, United States; [5]University of California, Los Angeles, Los Angeles, CA, United States; [6]University of California, San Francisco, San Francisco, CA, United States; [7]University of California, Davis, Sacramento, CA, United States; [8]City of Hope National Medical Center, Duarte, CA, United States; [9]Northwestern University, Chicago, IL, United States; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, United States; [11]Nanostring, Seattle, WA, United States; [12]California Institute of Technology, Pasadena, CA, United States*

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 at dose levels of 0.4, 1.2, or 4×10^9 NeoTCR-edited T cells.

Pre- and post-treatment blood and biopsy samples were collected to evaluate NeoTCR-P1 pharmacokinetics, tumor trafficking, signs of T cell engagement or potential mechanisms of resistance.

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 neoTCRs 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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