

Objective clinical response by KRAS mutation-specific TCR-T cell therapy in previously treated advanced Non-small cell lung cancer (NSCLC)

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Introduction

Solid tumors harbor clonal cancer gene mutations that generate tumor neoantigens. These can be presented by human leukocyte antigen (HLA) molecules to T-cell receptors (TCRs) expressed on T cells. We have developed non-viral TCR-T cells based on the *Sleeping Beauty* transposon/transposase system, which is faster and more cost-effective than other gene transfer technologies. These TCR-T cells are generated from a library of validated TCRs with defined specificity to frequent HLA alleles and hotspot mutations in *KRAS*, *TP53* and *EGFR*, which are common in solid tumors.

Study Design

This is a first-in-human phase 1/2 study of autologous TCR-T cell therapy in patients with non-small cell lung (NSCLC), colorectal, endometrial, pancreatic, ovarian and bile duct cancer. The phase 1 portion of the study explores up to four TCR-T dose levels. The primary objective of the phase 1 portion is to define the incidence of treatment related dose limiting toxicities (DLTs) and the recommended phase 2 dose to be explored in disease specific expansion cohorts.

Results

The first patient dosed in the phase 1 portion of the study was a 34-year-old female diagnosed with NSCLC. The patient had recurrence after left lower lobectomy and adjuvant platinum-based chemotherapy and progressed on three prior lines of systemic therapy including carboplatin/pemetrexed/pembrolizumab, durvalumab/tremelimumab/selumetinib and a SHP2 inhibitor with best response to prior therapy being partial response. The patient was germline for HLA-A*11:01 and we detected a *KRAS*^{G12D} mutation in the tumor. This corresponded to the specificity of one of the ten TCRs within the TCR library. Autologous TCR-T cells were produced by *Sleeping Beauty* transposition at cGMP and were released based on identity, specificity, functionality and sterility. Seven days after start of inpatient lymphodepletion (cyclophosphamide [60mg/kg for 2 days] and fludarabine [25mg/m² for 5 days]), the patient received a product containing 95% transgenic TCR and contained a total dose of 9x10⁹ TCR-T cells (Day 0). The patient experienced grade 2 cytokine release syndrome (CRS) from days 0 to 4, which resolved with nasal cannula oxygen supplementation and did not require anti-IL-6 treatment. Grade 4 thrombocytopenia and grade 3 anemia occurred on Days 3 and 4, respectively, both attributed to lymphodepletion chemotherapy. The patient's cell counts started to recover allowing discharge on Day 11. TCR-T cellular kinetics demonstrated a short redistribution phase followed by rapid expansion reaching peak (C_{max}) circulating TCR-T cells of 1,038 cells/μL by flow cytometry at Day 4, corresponding to 5x10⁵ copies/μg DNA by digital droplet PCR. TCR-T cell persistence was ongoing as of

Week 12 with the patient's total CD3⁺ cells comprising 22% TCR-T cells. Post-infusion serum cytokines demonstrated elevations of inflammatory cytokines (baseline vs peak) IL-8 (31.7 vs 595 pg/mL), TNF α (2.3 vs 4.0 pg/mL), GM-CSF (<limit of quantitation (LOQ) vs 18.9 pg/mL) and IL-6 (<LOQ vs 22.0 pg/mL), which correlated with onset and resolution of CRS. In contrast, IFN- γ , which was undetectable at baseline, increased following TCR-T infusion with a peak at Day 2 (606 pg/mL) and remained elevated through Day 10 (82.5 pg/mL). The patient was determined to have a confirmed partial response by RECIST v1.1 with regression of 46.3% in target lesions at Week 6, and 51.2% at Week 12. Confirmed regression of non-target lesions was also observed at weeks 6 and 12.

Conclusion

This is the first evidence of a confirmed objective response using TCR-T cells for treatment of advanced NSCLC. This is the first-in-human experience of *Sleeping Beauty* TCR-T cell therapy. No DLTs related to TCR-T cell product were observed, and treatment had a manageable safety profile. Significant persistence of TCR-T cells was observed at week 12. This clinical trial is open for enrollment of patients with advanced solid tumors harboring *KRAS*, *TP53* and *EGFR* mutations.