Background

Adaptive T-cell therapy is an emerging strategy for solid tumors. Cancer cells frequently harbor driver-mutations in KRAS, TP53, and EGFR genes that can be targeted by T-cell receptors (TCRs). These neoepitopes are presented on the tumor cell surface by human leukocyte antigen (HLA) molecules to TCRs. We have developed, using non-viral Sleeping Beauty transposition, a library of TCRs able to target KRAS, TP53 and EGFR mutations for the treatment of solid tumors. The Sleeping Beauty transposase/transposon system can be used as a non-viral gene transfer system in human cells. Sleeping Beauty transposase is briefly expressed to integrate the transposon into the genome and is then degraded and eliminated from the T cell. Sleeping Beauty transposon is inserted into TA dinucleotide repeats randomly within the human genome (Figure 1A). Co-transfer of Sleeping Beauty transposase and transposon into the T cell results in rapid and stable expression of the introduced neoantigen-specific TCR, which allows tumor cell recognition (Figure 1B). The Sleeping Beauty system has high flexibility, and low manufacturing time and cost compared to other gene transfer technologies.

Neoantigen-Specific TCR Development

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Study Design

This is a first in human phase 1/2 study of TCR-T cell therapy for patients with non-small cell lung, colorectal, endometrial, pancreatic, ovarian and bile duct cancer. Eligible patients have received and failed standard care of therapy for their tumor and have a mutation and HLA type match for a TCR in the library (Figure 2). After enrollment, patients will undergo leukapheresis, optional bridging therapy during manufacturing (Figure 3) and lymphodepletion. The protocol’s TCR-T cells will be administered to the patient intravenously following lymphodepletion. The starting dose will be 5 x 10^9 TCR-T cells (Dose Level 1 (DL1)), in the absence of a Dose Limiting Toxicity (DLT) escalating to 4 x 10^10 (DL2) and 1 x 10^11 TCR-T cells, as safety allows. After completion of DL2, an analysis of TCR-T cell persistence will be performed, and, if deemed necessary, interlevel-2 (I-L2) will be administered after the TCR-T cell infusion. The primary objective of the phase I portion is to define the incidence of the DLT and the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of TCR-T cells administered without IL-2 (Ann A) or with IL-2 (Ann B). Clinical and radiologic responses will be assessed by RECIST (v1.1) at six and 12 weeks after TCR-T cell infusion and every 12 weeks thereafter for up to two years or until study discontinuation, whichever occurs first. All patients will continue to be monitored in a long-term follow-up for up to 15 years post-TCR-T cell infusion (Figure 4). The study has been initiated and enrollment is ongoing.

Alayanous Therapeutics’ TCR Library - Figure 2

Study Population and Key Inclusion / Exclusion Criteria

Key Inclusion Criteria

- Patients with tumors that have somatic mutation(s) and HLA type restriction combination matching an available TCR as TCR library
- Patients who have previously received at least one line of standard systemic therapy for their advanced/metastatic cancer and have any form of personal immunodeficiency
- Patients who have previously received at least one line of standard systemic therapy for their advanced/metastatic cancer and have either progressed, recurred, or were intolerant to prior treatment

Key Exclusion Criteria

- Concurrent systemic steroid therapy at a dose of >10 mg prednisone daily or equivalent is excluded.
- Any form of primary immunodeficiency
- Patients who have previously received at least one line of standard systemic therapy for their advanced/metastatic cancer and have any form of personal immunodeficiency
- Patients who have previously received at least one line of standard systemic therapy for their advanced/metastatic cancer and have any form of personal immunodeficiency

Summary

- Applying the clinical Sleeping Beauty transposase/transposon gene transfer platform. Sleeping Beauty is utilized to genetically modify the patient’s own T cells (both CD4+ and CD8+) using the TCR plasmid.
- The major advantage of using non-viral vectors is in its potential bio-safety (e.g., minimizing insertional mutations/possible secondary malignancies)
- Non-viral vectors have also shown significant attention due to their lower immunotoxicity.
- Phase I portion of the study is expected to complete accrual by the end of 2023
- Phase II portion will include expansion cohorts of non-small cell lung, colorectal, endometrial, pancreatic, ovarian, and bile duct cancer

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Study Design - Figure 4

Figure 1. A) Transposon / transposase system for integration into T cell DNA; B) tumor neoantigen recognition by transposed T cell receptor.

Figure 3: Manufacturing process of autologous TCR-T cell drug product

Figure 2 Subgroup 4: NSCLC: Subjects with recurrent and/or metastatic disease with disease progression or intolerance to treatment with a PD-1/PD-L1 inhibitor either as a single agent, or in combination with other immune checkpoint inhibitors (e.g., CTLA-4 inhibitors), and/or platinum-doublet chemotherapy. Subjects with targetable oncogene alterations (e.g., EGFRI, ALK, ROSI, RET, NTRKI-5, SMRT) must have had disease progression or intolerance to at least one prior line of targeted therapy.

Figure 4 Subgroup 5: Cholangiocarcinoma: Subjects must have histologically confirmed cholangiocarcinoma stage II, III, or IV (extrahepatic, extrahepatic and perihilar) that is not eligible for curative resection, transplantation, or ablative therapies, and who have advanced/recurrent disease (includes adjuvant chemotherapy and/or chemo-radiation; prior hormonal therapy not included).