Trial in progress: A phase 1, first-in-human clinical trial for T-Plex, a multiplex, enhanced T cell receptor-engineered T cell (TCR-T) therapy for solid tumors

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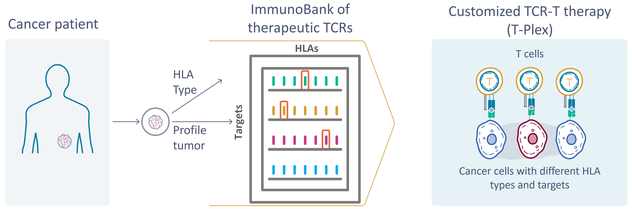
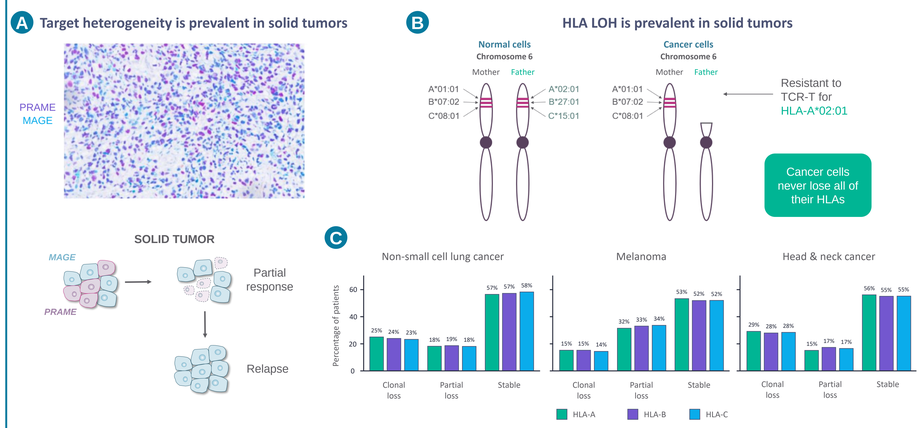
Abstract # 1900

Background and Rationale

- Advanced solid tumor malignancies are difficult to conquer due to complex biology
- Lack of sufficient endogenous anti-tumor T cells hinders the immune response, even in the presence of checkpoint inhibitors
- T cells engineered with exogenous T cell receptors (TCR-Ts) can target tumor specific antigens presented on HLAs to kill tumor cells
- However, solid tumors are notoriously heterogenous with variable target antigen expression, and may also have HLA loss of heterozygosity (LOH) in up to 40% of tumors, a common resistance mechanism to avoid immune detection
- First-generation TCR-Ts targeting single antigens had limited response rates (30-50%) and short durations of response (3-4 months), possibly due to tumor target heterogeneity and HLA LOH, an immuno-suppressive tumor microenvironment, poor TCR-T persistence and/or TCR-T exhaustion.
- Our solution is to administer multiple enhanced TCR-Ts targeting different shared antigens commonly expressed in solid tumors presented on diverse and frequent HLA types (T-Plex).
- TCR-Ts are enhanced with co-delivery of CD8α/β and a dominant negative TGFβ receptor to enable potent tumor killing and long-term persistence

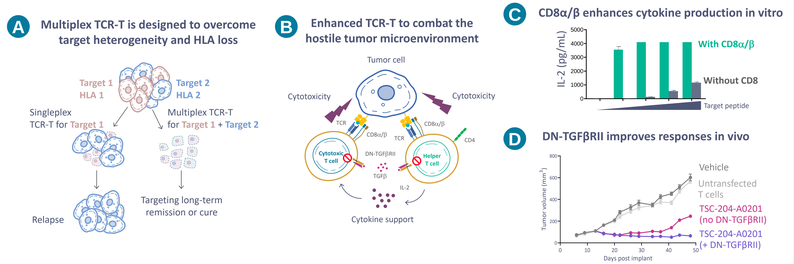


Heterogeneity in Solid Tumors Limits the Efficacy of Singleplex Therapies



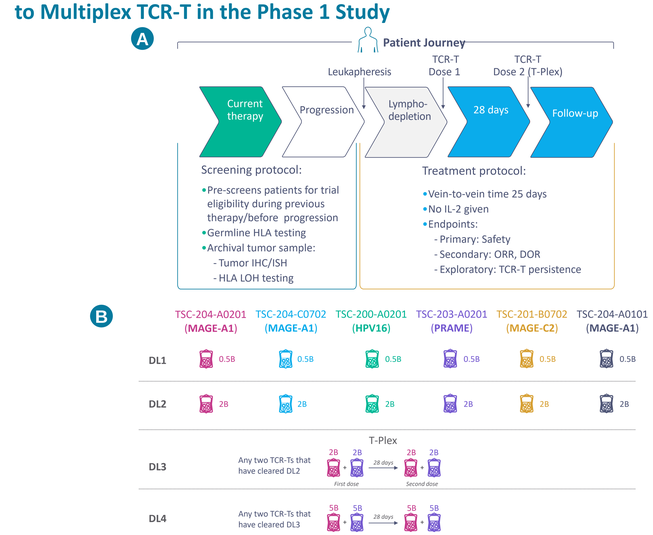
(A) Melanoma samples were stained with PRAME (purple) and MAGE-C2 (blue) antibodies. Tumor cells were noted to be positive for either PRAME or MAGE-C2 or both. Targeting single antigens, for example PRAME, could result in partial responses followed by eventual disease progression. (B) HLA LOH generally occurs through loss of an HLA haplotype on chromosome 6. (C) Novel pan-HLA LOH detection algorithm using tumor/normal comparisons of Tempus tumor data indicate that clonal and sub-clonal loss of HLA occurs in ~15-30% of common solid tumors (Nayar et al SITC 2023). Tumors that have lost the target HLA cannot respond to TCR-T therapy, however cancer cells never lose all their HLAs. Prospective screening for LOH allows for selection of TCR-Ts targeting intact HLAs only. Administration of multiplex TCR-Ts, with targets on HLAs from both haplotypes, may prevent tumor escape due to the emergence of LOH during treatment.

Multiplex, Enhanced TCR-T Therapies May Improve Responses in Solid Tumors



(A) First-generation TCR-Ts targeting single antigens on single HLA types often result in partial responses and rapid progression. Administration of multiplexed TCR-T targeting different target antigens on different HLA types has the potential to induce more durable or even complete responses. (B) TCR-Ts are enhanced with co-delivery of CD8α/β to engage helper T cells and a dominant negative TGFβ receptor (DN-TGFβRII) to enhance T cell expansion/persistence. (C) CD4+ T cells engineered to express TCR+CD8α+CD8β coreceptors had ~100-fold higher cytokine production versus CD4+ cells expressing TCR only. (D) Expression of dominant-negative TGFβRII (DN-TGFβRII) in a xenograft mouse model demonstrates more durable responses *in vivo*. NCG mice implanted with human U266B1 tumors were randomized and received two doses of TSC-204-A0201 TCR-T cells ± DN-TGFBRII, untransfected control T cells, or vehicle control (PBS). Tumor volumes were measured twice weekly.

Pre-identification of Patients and Dose Escalation Scheme Provides a Rapid Path to Multiplex TCR-T in the Phase 1 Study



(A) Patients with melanoma, NSCLC, head and neck cancer, cervical cancer, ovarian cancer, anogenital cancers or other solid tumors with a reasonable likelihood of target expression are eligible. Screening includes germline HLA typing then archival tumor testing for antigens and HLA LOH any time during standard anticancer treatment. Treatment involves one to two doses of TCR-T therapy after lymphodepletion.
(B) INDs have been cleared for six TCR-Ts targeting: MAGE-A1 on HLA-A*02:01 (TSC-204-A0201), HLA-C*07:02 (TSC-204-C0702), and HLA-A*01:01 (TSC-204-A0101); HPV16 on HLA-A*02:01 (TSC-200-A0201); PRAME on HLA-A*02:01 (TSC-203-A0201); and MAGE-C2 on HLA-B*07:02 (TSC-201-B0702) and their combinations (T-Plex). As additional IND applications are cleared, they will be incorporated into the same study and follow the same dose escalation scheme.

Key Inclusion/Exclusion Criteria and Specifications for Study NCT05973487:

Inclusion Criteria

- Age ≥ 18, all genders
- Diagnosis of advanced melanoma, non-small cell lung cancer, head and neck cancer, ovarian cancer, cervical or anogenital cancers, or other solid tumors with reasonable chance of expressing 1 or more relevant targets
- Failure of standard of care, including any relevant targeted therapy or checkpoint inhibitor
- At least 1 HLA with a TCR-T match and no LOH of that HLA in the tumor
- At least 1 target match
- At least 1 measurable lesion per modified RECIST v1.1
- ECOG PS 0-1 with adequate organ function

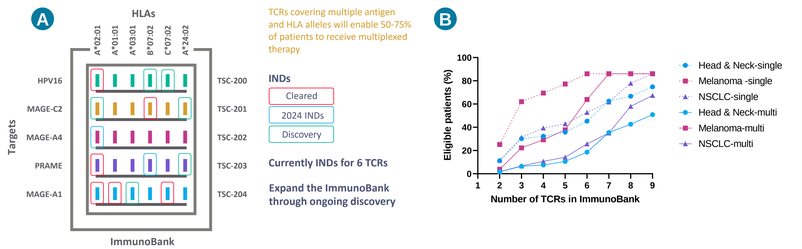
Exclusion Criteria

- CNS metastases that are symptomatic or in need of treatment; carcinomatous meningitis
- Major cardiac pathology or stroke/TIA within 12 months of enrollment
- Systemic corticosteroids within 7 days of enrollment
- Concurrent therapy that has not yet met washout requirements
- Hypersensitivity to fludarabine, cyclophosphamide, or study drug components
- Presence of an HLA type that may interfere with the HLA type being targeted

Protocol Specifications

- Lymphodepletion: Cyclophosphamide (60 mg/kg on Days -7 and -6); fludarabine (30 mg/m2 on Days -7 to -3)
- Hospitalization of 1st three singleplex and 1st three T-Plex patients for 3-7 days post cell infusion

Eligibility for Multiplex Therapy Increases with Growing Collection of TCR-Ts



(A) The ImmunoBank is the collection of TCR-Ts from which one to two therapies for individual patients are chosen. IND applications for six TCR-Ts and the T-Plex combination have been cleared. Two additional IND applications are on track to be submitted by end-2024. (B) As the number of TCR-T choices grows, the number of solid tumor patients eligible for singleplex therapy (dotted lines) or multiplex therapy (solid lines) increases.

For Additional Information:

NCT05812027: A Screening Study to Collect Samples for TAA, HLA & HLA Loss of Heterozygosity in Patients With Metastatic Solid Tumors
NCT05973487: A Basket Study of Customized Autologous TCR-T Cell Therapies in Patients With Locally Advanced (Unresectable) or Metastatic Solid Tumors
NCT05473910: A Study of TSC-100 and TSC-101 in AML, ALL and MDS Patients Undergoing Haploidentical Donor Transplantation
Please contact the Clinical team at: clinicaltrials@tscan.com or Investor Relations at: IR@tscan.com

Additional TScan Presentations

Oral Presentation:
#419: Discovery of Tumor Reactive TCRs and their Cognate Antigenic Targets via High-Throughput Functional Screening on Sat, May 11, 2024 at 11:15 AM
Poster Presentations:
#1901: Trial in Progress: A Phase 1 Trial of TSC-100 and TSC-101, Engineered T Cell Therapies That Target Minor Histocompatibility Antigens to Eliminate Residual Disease After Hematopoietic Cell Transplantation
#834 Nonclinical Development of T-Plex Component TSC-204-A0101: A Natural TCR-T Cell Therapy for the Treatment of MAGE-A1- and HLA-A*01:01-Positive Cancers
#835 Non-Clinical Development of T-Plex Component TSC-201-B0702: A TCR-T Cell Therapy Directed to a Novel HLA-B*07:02 Restricted MAGE-C2 Epitope for the Treatment of Solid Tumors