Initial Data From a Phase 1, First In Human Clinical Trial For T-Plex, A Multiplexed, Enhanced T Cell Receptor-Engineered T Cell (TCR-T) Therapy For Solid Tumors

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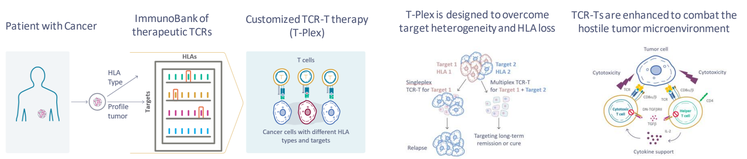
Abstract # CT170

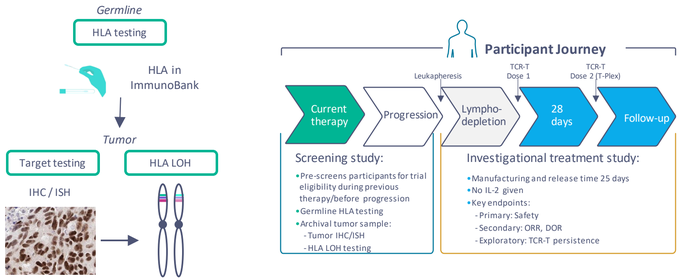
Background and Rationale

- Advanced solid tumor malignancies are difficult to cure due to complex biology.
- Lack of sufficient endogenous anti-tumor T cells hinders an 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 human leukocyte antigens (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).
- The 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 which should enable potent tumor killing and long-term persistence.
- Product and study design details were presented at ASCO 2023 (Abstract #2554).
- Initial data from the screening study are reported here.



Prospective Identification of Target and HLA Expression is Designed to Maximize Speed Within the Participant Journey

- The **screening study (NCT05812027)** evaluates participants with solid tumors to determine germline HLA types, target expression and tumor HLA/LOH status.
- Pre-identification of participants allows for potential rapid enrollment into the **investigational treatment study (NCT05973487).**



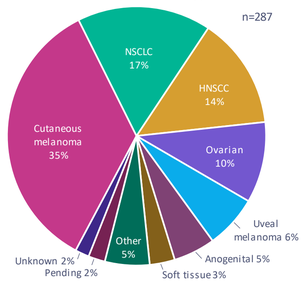
- 302 participants were enrolled into the screening study across 14 sites since Sept 2023.

Participant Demographics (n=287)		
Age	Median	63
	Range	21-85
Gender	Male	132 (46%)
	Female	156 (54%)
Race	White or Caucasian	230 (80%)
	Black or African American	12 (4%)
	Asian	6 (2%)
	Hispanic or Latino	3 (1%)
	American Indian or Alaskan Native	2 (1%)
	Other or Unknown	34 (12%)

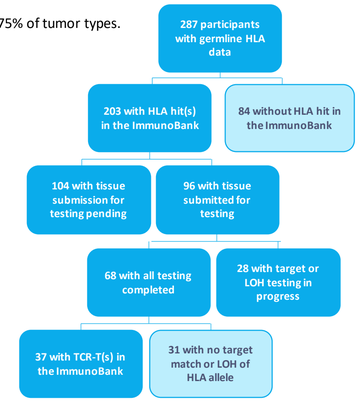
Demographics and Sample Testing Schema

- Participants enrolled into the screening study with a variety of solid tumors.
- Germline HLA data were available for 287 participants as of the 8 May 2024 data cut.
- Melanoma, non-small cell lung cancer, head and neck cancer, and ovarian cancer account for >75% of tumor types.

Participants in the screening protocol have a broad array of tumor types

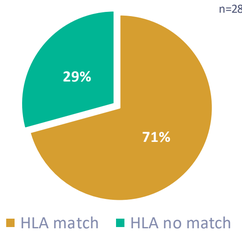


Additional tumor types include anogenital cancers, sarcomas, breast cancers, thyroid cancer, esophageal cancer, osteosarcoma, uterine cancers and meningioma.

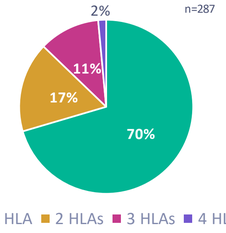


The Majority of Participants Have At Least One TCR-T Match in the ImmunoBank , and Many Have Multiple TCR-T Matches that Could Qualify for T-Plex

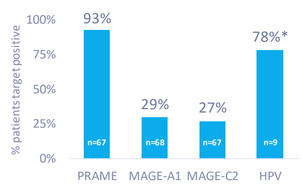
71% of participants have at least one HLA match to the ImmunoBank



30% of patients have >1 HLA match to the ImmunoBank

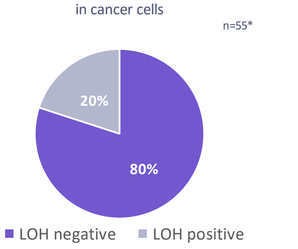


>90% of patients are positive for targets in the ImmunoBank



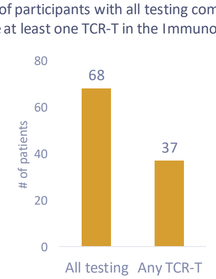
*Testing only in indications associated with HPV
Note: Target testing is prioritized based on HLA if samples are limited

80% of participants exhibit intact HLA haplotypes in cancer cells

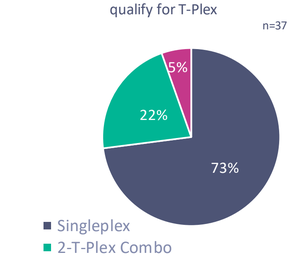


*Samples that are negative for target/HLA match or are homozygous for the targetable HLA allele are not submitted for LOH testing

>50% of participants with all testing completed have at least one TCR-T in the ImmunoBank



27% of participants with TCR-T match that could qualify for T-Plex



Key Inclusion/Exclusion Criteria and Specifications for Study NCT05973487

Inclusion Criteria

- Age ≥ 18, all genders
- Diagnosed advanced melanoma, non-small cell lung cancer, head and neck cancer, ovarian cancer, cervical or anogenital cancers, or other solid tumors that may express relevant targets
- Failure of standard of care, including any relevant targeted therapy or checkpoint inhibitor
- ≥ 1 HLA with a TCR-T match and no LOH of that HLA in the tumor
- ≥1 target match
- ≥ 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 seven 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 first three singleplex and first three T-Plex patients for three to seven days post cell infusion

Dose Escalation Scheme Provides a Path to Multiplex TCR-T in the Phase 1 Study

- TCR-Ts currently in the master protocol target PRAME on HLA-A*02:01; HPV16 on HLA-A*02:01; MAGE-A1 on HLA-A*02:01, HLA-A*01:01, or HLA-C*07:02; or MAGE-C2 on HLA-B*07:02.
- All TCR-Ts in the ImmunoBank and master protocol are first tested as singleplex therapies in dose levels 1 and 2 before becoming **available for multiplexing in dose levels 3 and 4.**

Conclusions and Acknowledgements

- The screening study is underway and widely adopted, with over 300 participants enrolled.
- >50% of participants with all testing completed (n=68) have at least one TCR-T in the ImmunoBank and 27% of those could qualify for T-Plex.
- Potential participants have been pre-identified across all six singleplex cohorts, as well as some T-Plex cohorts (n=37 and n=10, respectively).
- Eligibility for T-Plex is expected to increase as the ImmunoBank grows via additional IND applications.
- The **first participant** (with metastatic cutaneous melanoma) was dosed with TSC-203-A0201 targeting PRAME; no acute toxicities were observed.
- Manufacturing for three additional participants is underway.

We extend a warm thank you to the participants, families and treatment teams associated with the screening and investigational treatment studies.

For more information, please contact: clinicaltrials@tscan.com