### Background and Rationale

- Most patients fail checkpoint immunotherapy due to lack of sufficient endogenous anti-tumor T cells
- A potential solution is to engineer T cells with exogenous T cell receptors (TCRs) that target tumor antigens
- However solid tumors are notoriously heterogenous with heterogeneous target antigen expression
- Solid tumors have also been recently recognized to have HLA loss of heterozygosity (LOH) in up to 40% of tumors
- First generation TCR-Ts targeting single antigens had limited response rates (30-50%) and short durations of response (3-4 months)
- TScan’s solution is to develop multiplexed TCR-Ts targeting different antigens on different HLA types
- TCR-T cells also have genetic enhancements to enable potent tumor killing and long-term persistence.

### Multiplexed TCR-T cell therapy (T-Plex) can effectively address tumor heterogeneity and HLA LOH

1. Prevent progression
2. Prospectively select patients

#### TScan’s solution for increasing duration of response
- Prevent progression
- Prospectively select patients
- Increase response rates
- Enhance persistence

#### Target Heterogeneity in Solid Tumors

- Melanoma samples were stained with PRAME (purple) and MAGE-C2 antibodies (blue)
- Tumor cells were noted to be positive for either PRAME or MAGE-C2 or both
- Targeting single antigens is expected to result in partial responses in these tumors with rapid progression.

### HLA loss of heterozygosity (LOH) is prevalent and overlooked in solid tumors

(A) HLA loss of heterozygosity (LOH) generally occurs through loss of an HLA haplotype on chromosome 6.

(B) Novel pan-HLA LOH detection algorithm using tumor normal comparisons. Tempus tumor data indicate that clinical and sub-clinical loss of HLA occurs in ~15-20% of common solid tumors. Tumors that have lost the target HLA cannot respond to single-targeted TCR-Ts.

### Screening protocol pre-identifies patients eligible for treatment

#### Cancer Diagnosis
- 1st line regimen
- 2nd line regimen

#### Lesions
- Lesions
- Lymph node

#### T-Plex dose 1
- T-Plex dose 2
- T-Plex dose 3
- T-Plex dose 4

### Rapid dose escalation path to multiplexing from dose level 3

- Any two TCR-Ts that have cleared DL(p)
- Any two TCR-Ts that have cleared DL(2)
- T-Plex

### Eligibility for multiplexed therapy increases with growing collection of TCR-Ts

(A) The ImmunoBank is the collection of TCR-Ts from which 1-2 therapies for individual patients are chosen. INDs for TCR-TTs and the T-Plex combination have been closed. Two additional INDs are on track to be submitted by end-2023. (B) As the number of TCR-T choices grows, the number of solid tumor patients eligible for singleplexed therapy (dotted lines) or multiplexed therapy (solid lines) increases.

*For more information on TScan’s ImmunoBank, see abstracts:
# 357: Discovery of a novel MAGE2 epitope for TCR-T adoptive cell therapy from expanded T cell clones of TIL therapy products
# 364: Non-clinical development of T-Plex component TSC-200 A0201: A natural HPV16 E7 specific TCR-T cell therapy for the treatment of HPV16 positive solid tumors
# 376: Overcoming tumor heterogeneity - Clinical trial assays to prospectively assign patients customized multiplexed TCR-T cell therapy in Phase 1
# 390: Discovery of MAGE-A1 specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors*