Product characteristics and clinical trial design for T-Plex: Multiplexed, enhanced T cell receptor-engineered T cell therapy for solid tumors

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**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 heterogeneous 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.

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

- **A** HLA loss of heterozygosity (LOH) generally occurs through loss of one HLA haplotype on chromosome 6.
- **B** Novel HLA-LOH detection algorithm using tumor/normal comparisons of Tempus tumor data identifies HLA clonal loss in 15-30% of common solid tumors. Those tumors cannot respond to single-targeted TCR-Ts.
- **C** HLA loss of heterozygosity (LOH) generally occurs through loss of one HLA haplotype on chromosome 6.

**Multiplexing and TCR-T selection overcome heterogeneity and HLA LOH**

- **1)** Prevent Progression: First-generation TCR-Ts targeted single antigens on single HLA types in partial responses and rapid progression. Multiplexing TCR-Ts targeting different target antigens on different HLA types has the potential for complete responses and long-term remissions.
- **2)** Prospectively select patients: Germline HLA typing is followed by testing tumors for antigens and HLA LOH. TCR-T selection can be used to overcome HLA LOH.

**Target heterogeneity in solid tumors**

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

**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 two TCR-Ts and the TPlex combination have been cleared. Two additional INDs for TCR-Ts targeting HPV16 and PRAME are cleared, they will follow the same dose escalation scheme.
- **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.

**Dose escalation scheme provides rapid path to multiplexing from dose level 3**

- **A** INDs have been cleared for TCR-Ts targeting MAGE-A1 on HLA-A*02:01 (TSC-204-A0201), HLA-C*07:02 (TSC-204-C0702) and their combination. The FDA cleared protocol allows multiplexing and repeat dosing from dose level 3. As additional INDs for TCR-Ts targeting HPV16 and PRAME are cleared, they will follow the same dose escalation scheme.

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

- **A** Patients with melanoma, non-small cell lung cancer, head and neck cancer, cervical cancer, ovarian cancer or anogenital cancers are eligible. Screening includes germline HLA typing then archival tumor testing for antigens and HLA LOH any time during standard cancer treatment. Treatment involves 1-2 doses of TCR-T cell therapy after lymphodepletion.