TRIAL IN PROGRESS: PRODUCT CHARACTERISTICS AND CLINICAL TRIAL DESIGN FOR T-PLEX, A MULTIPLEXED, ENHANCED T CELL RECEPTOR-ENGINEERED T CELL THERAPY FOR SOLID TUMORS

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Background

Checkpoint immunotherapies have revolutionized solid tumor treatment yet durably benefit a minority of patients, as they rely on endogenous anti-tumor T cells. A potential solution for patients lacking functional endogenous anti-tumor T cells is engineering their T cells with exogenous T cell receptors (TCRs) to target and kill tumor cells. Initial clinical trials with TCR engineered T cell therapies (TCR-Ts) produced partial, short-lasting responses because they targeted single tumor antigens. Solid tumors are notoriously heterogeneous with highly variable antigen expression. Recent discoveries also identified HLA loss of heterozygosity occurring in up to 40% of solid tumors, allowing tumor cells to evade T cell attack.

To overcome this heterogeneity, TScan has developed T-Plex, a multiplexed cell therapy comprising 2–3 different TCR-Ts, chosen from a collection of TCR-Ts called the ImmunoBank, to target different tumor antigens on different HLA types with confirmed tumor expression. To deepen clinical responses, TCR-T cells are engineered to express CD8αβ co-receptors that, in preclinical experiments, enable CD4+ helper T cells to have >100-fold improved cytotoxicity and cytokine secretion. Finally, to allow T cell persistence despite immunosuppressive TGF-β in tumor microenvironments, TCR-T cells also express the dominant negative TGF-β receptor, enabling ~10-fold improved proliferation despite the presence of TGF-β. These additional genes can be included because of a proprietary transposon vector with larger cargo limit.

Methods

The Phase 1 study utilizes a separate screening protocol to identify patients any time during standard clinical care, enabling rapid enrollment into the treatment protocol upon disease progression. Screening comprises germline HLA testing, then archival tumor testing for antigen expression and HLA loss. Treatment includes standard lymphodepletion followed by one or 2 doses of T-Plex infused 28 days apart. Dose escalation starts with testing single TCR-Ts in dose levels 1 and 2. Thereafter, TCR-Ts are combined and escalated in dose levels 3 and 4. TCR-Ts initially in the master protocol target MAGE-A1 or HPV16 on HLA-A*02:01 or MAGE-A1 on HLA-C*07:02. Additional TCR-Ts added to the ImmunoBank and master protocol go through dose levels 1 and 2 as single therapies before becoming available for multiplexed dose levels 3 and 4. Primary endpoints include safety and feasibility, secondary endpoints are rates and durations of response and exploratory endpoints measure T cell persistence. Three additional TCR-Ts are on track to be added to the ImmunoBank in 2023, that could allow 50–80% of common solid tumor patients to qualify for multiplexed TCR-T therapy.

Trial Registration

NCT05812027

Ethics Approval

The study obtained ethics approval from WCG-IRB (20230668 and 20230670). Participants give/will give informed consent before taking part.