Background Engineered T cell therapies such as CAR-T cell therapies have transformed the treatment of B-cell but not non-B cell hematologic malignancies. Allogeneic hematopoietic cell transplantation (HCT) remains the best curative option for hematologic malignancies but ~40% of patients relapse post-HCT with up to 90% mortality due to residual disease post-HCT. A key challenge in non-B cell malignancies is identifying the right antigens for T cell targeting. Cancer-associated antigens are heterogeneous, enabling rapid escape of malignant cells with low antigens, while targeting lineage-specific antigens without distinct expression in malignant versus normal myeloid cells can cause prolonged neutropenia. 

A potential solution is targeting minor histocompatibility antigens (MiHAs) that are homogeneously expressed on all hematopoietic cells and are genetically mismatched between donors and patients undergoing HCT. These mismatches enable T cells to selectively eliminate residual patient hematopoietic cells, normal or malignant, leaving donor cells untouched. TScan has developed allogeneic donor derived T-cell products TSC-100 and TSC-101, targeting MiHAs HA-1 and HA-2 respectively, both presented on HLA-A*02:01. By choosing HCT patients who are HLA-A*02:01 positive (>98% of whom are either HA-1 or HA-2 positive) and donors who are either HLA-A*02:01 or MiHA negative, TSC-100 or TSC-101 can potentially eliminate all residual patient-derived hematopoietic cells after HCT, sparing donor cells, to prevent disease relapse.

Methods Study NCT05473910 is a multi-center, multi-arm, non-randomized controlled Phase 1 umbrella study evaluating the feasibility, safety and preliminary efficacy of TSC-100 and TSC-101. Inclusion criteria (figure 1) include adults with AML, MDS or ALL eligible for reduced intensity conditioning-based haploidentical donor transplantation from HLA or MiHA mismatched donors. HLA-A*02:01-positive patients undergo HA-1/HA-2 testing and are assigned to either TSC-100 or TSC-101 treatment arms in addition to HCT. HLA-A*02:01-negative patients in the control arm receive HCT alone. Upon count recovery after HCT, patients in treatment arms receive either TSC-100 or TSC-101, administered as single or two doses. Primary endpoints include adverse event profiles and dose limiting toxicities. Secondary endpoints include relapse rates, disease-free survival and overall survival. Exploratory endpoints include surrogates of efficacy such as minimal residual disease (MRD) rates and donor chimerism kinetics. MRD is measured before and after HCT using flow cytometry, NGS and ddPCR. Donor chimerism is measured by standard STR-based and novel high-sensitivity NGS-based assays to quantify residual patient-derived hematopoietic cells. Together, these assays measure elimination of residual patient hematopoietic cells, malignant or normal, and could provide early evidence of biological activity.

Trial Registration NCT05473910

ETHICS APPROVAL
The study obtained ethics approval from WCG-IRB (20220488). Participants will give/have given informed consent before taking part.

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