Trial in Progress: A Phase 1 Trial of TSC-100 and TSC-101, Engineered T Cell Therapies That Target Minor Histocompatibility Antigens to Eliminate Residual Disease After Hematopoietic Cell Transplantation

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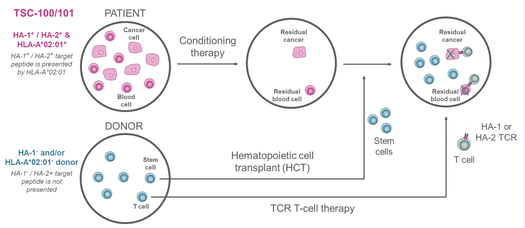
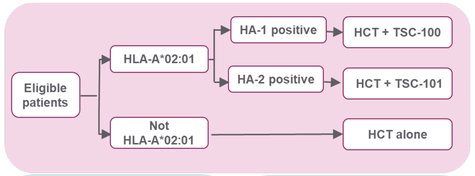
Background and Rationale

- Myeloid malignancies such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and certain acute lymphoblastic leukemias (ALL) have not been addressed by CAR-T therapies due to lack of targets specific for malignant myeloid cells that spare normal myeloid cells
- Hematopoietic cell transplantation (HCT) is the curative option for most of these patients yet ~40% of patients relapse after HCT due to residual malignant cells post-HCT
- A potential solution is to target minor histocompatibility antigens(MiHAs) mismatched between patients and donors
- The TSCAN-001 trial is studying TCR-Ts engineered to target MiHAs HA-1 (TSC-100) or HA-2 (TSC-101) to eliminate residual recipient blood cells post-HCT, thus preventing relapse
- Donor hematopoietic cells negative for MiHAs or HLA-A*02:01 that presents these MiHAs are untouched by TCR-T cells, thereby sparing normal blood cells post-HCT



Multi-arm Phase 1 trial design



Key Inclusion Criteria:

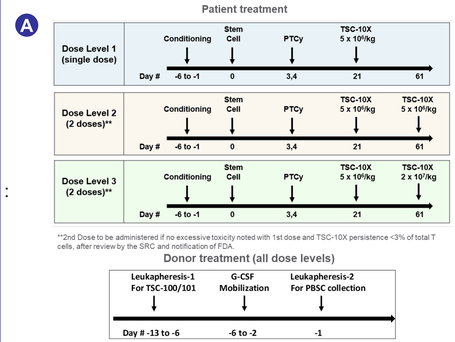
1. Age ≥18 years
2. AML, MDS or ALL
3. Reduced intensity conditioning HCT eligible
4. Haploidentical donors

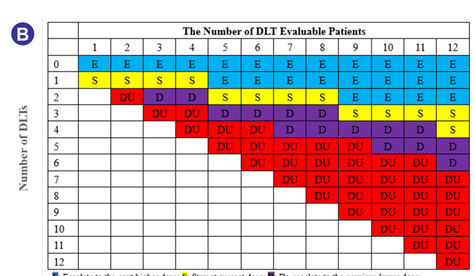
Key Endpoints:

1. Adverse events, DLTs
2. Relapse rates, DFS, OS
3. MRD pre-/ post-HCT, donor chimerism kinetics

- AML, MDS, ALL patients eligible for reduced intensity conditioning (RIC)-based haploidentical donor HCT are assigned to treatment arms if HLA-A*02:01 positive or control arm if HLA-A*02:01 negative
- In treatment arms, HA-1 positive patients (60%) get TSC-100 + HCT, HA-2 positive patients (40%) get TSC-101 + HCT and control arm patients get HCT alone
- Previous CIBMTR analysis found no differences in outcomes by HLA type (ASH 2021, abstract # 3863)

Dose escalation scheme and interval 3+3 dose escalation rules





(**A**) Dose level cohorts and treatment regimen for donors & patients in treatment arms. (**B**) interval 3+3 design has flexible cohort size from 1-12 participants depending on DLTs at each dose level (Liu et al, J Biopharm Stat., 2020)

Patients have been enrolled into all three arms of the study

	TSC-101	TSC-100	Control	
Patient ID	P-004-0001	P-004-0004	P-002-0001	P-007-0001
Diagnosis	MDS with mTP53	T-ALL	MDS	MDS
Molecular features	5q-, mTP53	ATM <2%	Trisomy 8	None
Pre-HCT MRD	**Positive** (TP53 VAF 67%)	Negative	**Positive** (SRSF2 VAF 35%)	Negative
RIC regimen	Flu/ Mel/ TBI	Flu/ Cy/ TBI	Flu/ Cy/ TBI	Flu/ Cy/ TBI
Transplant date	16 Feb 2023	21 Mar 2023	01 Nov 2022	03 Feb 2023
TCR-T treatment	09 Mar 2023	19 Apr 2023	N/A	N/A

Safety Review Committee (SRC) has approved escalation to Dose Level 2 for TSC-101

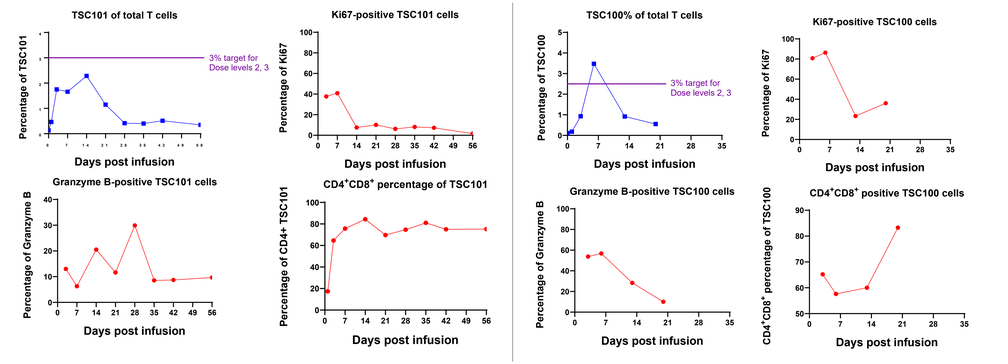
Adverse events and serious adverse events (SAEs) similar between arms

≥Grade 2 adverse event	TSC-101/ 100 Highest grade	Control Highest grade
Diarrhea	3	2
Anemia	3	4
Fatigue	2	2
Thrombocytopenia	4	4
Vomiting	2	2
Neutropenia	4	4
Hypertension	2	3
Hypomagnesemia	2	1
Skin/GI GVHD	3	3

Arm	SAE	Grade	Days post-HCT
Control	Skin GvHD	2	+49
Control	GI GvHD	3	+53
Control	Pneumonia	3	+56
TSC-101	GI GvHD	3	+67

No evidence of cytokine release syndrome or neurotoxicity noted to date after TSC-101/ TSC-100 infusion by clinical or laboratory monitoring (CRP/ ferritin)

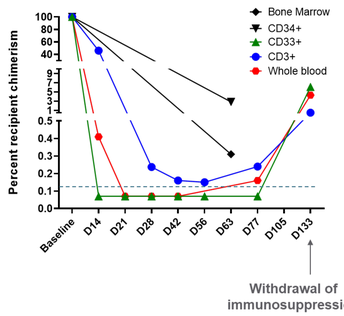
TSC-101 and TSC-100 undergo expansion, activation & persistence post-infusion



TSC-101 (left 4 graphs) and TSC-100 (right 4 graphs) show expansion (percent of T cells), proliferation (Ki67 positive), activation (granzyme B positive) and shift to CD4+ subsets that can persist long-term (Melenhorst et al, Nature 2022)

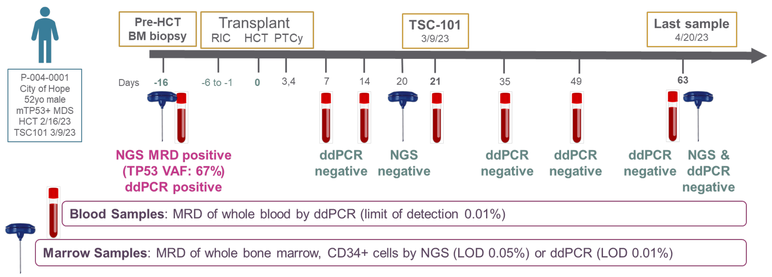
TSC-101 treated patient has undetectable recipient chimerism, unlike controls

Day post HCT	Subset	P-004-0001 (TSC-101)	P-002-001 (Control)	P-007-0001 (Control)
Day 21	CD33	UD	UD	D
	CD3	TSC-101→ D	D	D
	Whole blood	D	UD	D
Day 35	CD33	UD	UD	D
	CD3	D	D	UD
	Whole blood	D	UD	D
Day 42	CD33	UD	UD	D
	CD3	UD	D	D
	Whole blood	UD	UD	D
Day 56	CD33	UD	UD	D
	CD3	UD	D	UD
	Whole blood	UD	UD	D
Day 63	Whole bone marrow CD34		D D	
Day 77	CD33		UD	
	CD3		D	
	Whole blood		D	
Day 133	CD33		D	
	CD3		D	
	Whole blood		D	



UD: undetectable, **D**: detectable; chimerism measured with high-sensitivity Alloheme assay (limit of detection 0.13%)

TP53 mutant MDS patient turned from MRD(+) to MRD(-) after HCT & TSC-101



TP53 mutated MDS has >80% risk of relapse or death after HCT (Lindsley et al, NEJM 2017). Achieving MRD negative status and undetectable recipient chimerism is generally associated with low risk of relapse (Craddock, J Clin Oncol 2021).