

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



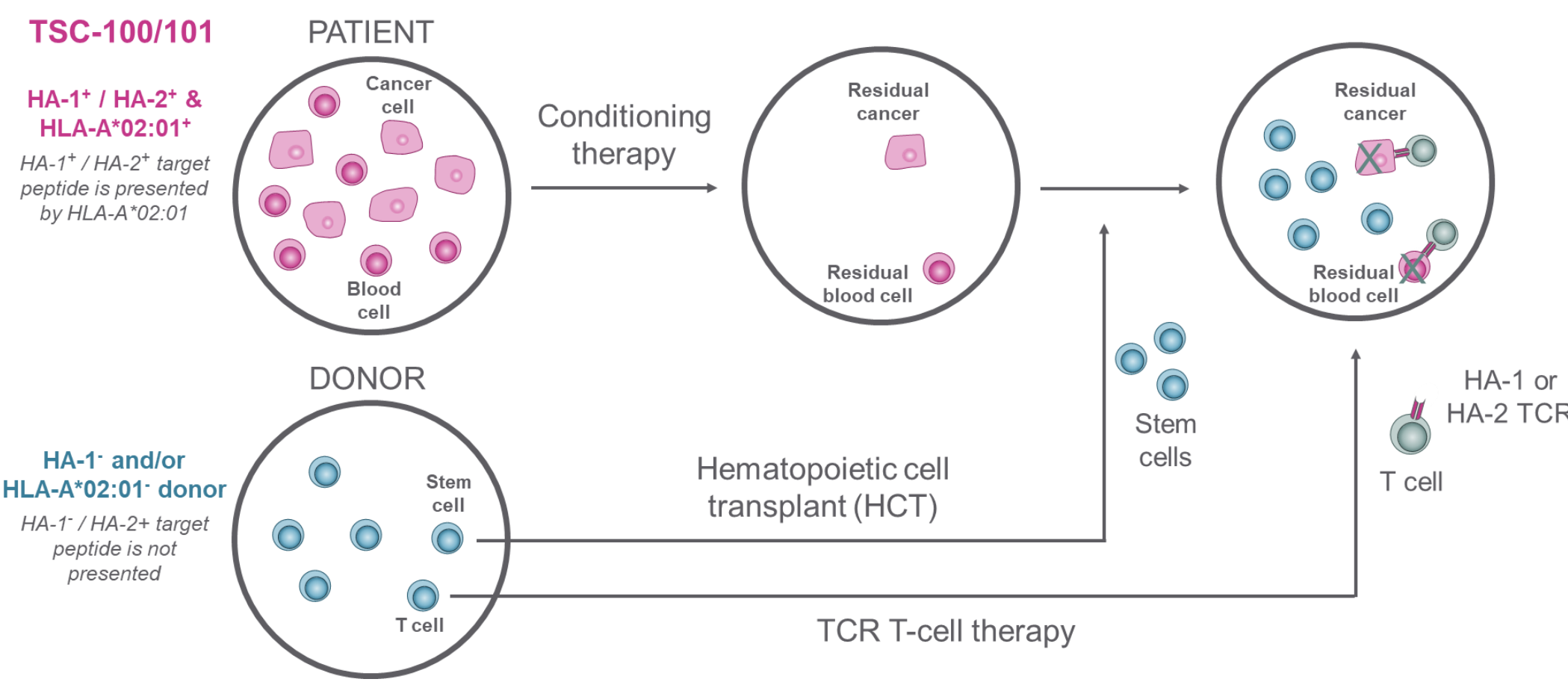
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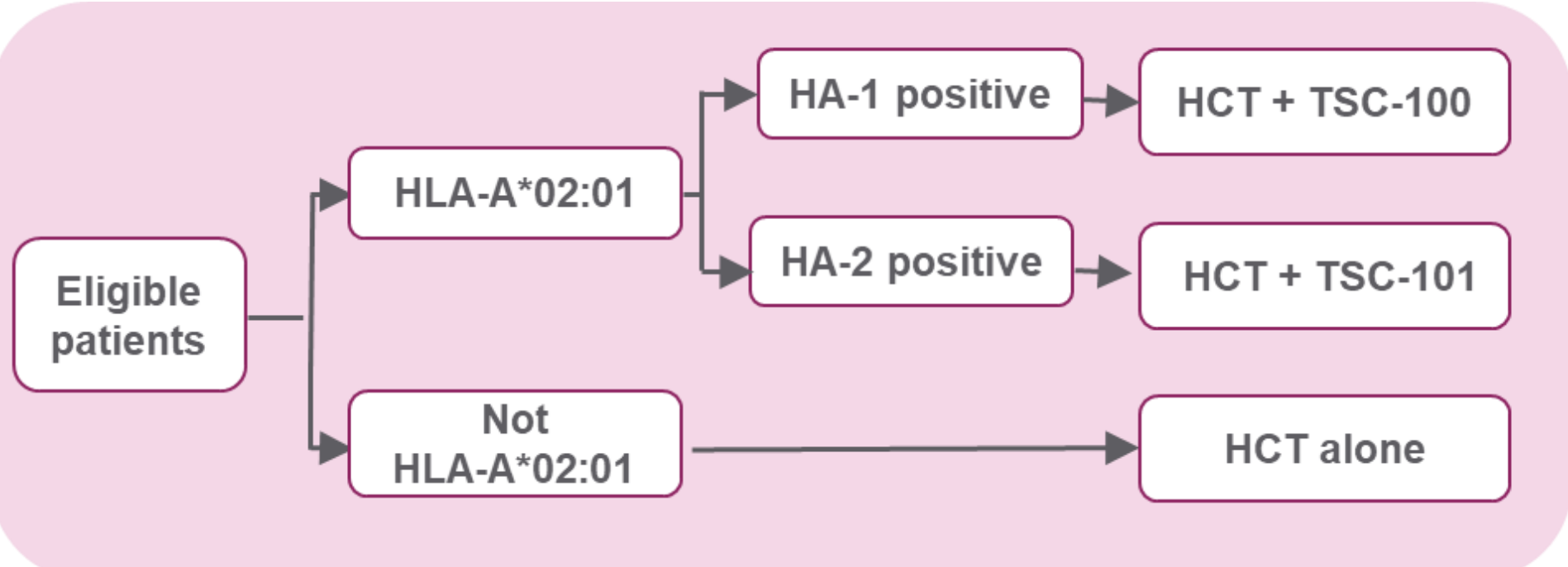
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Background and Rationale

- 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:

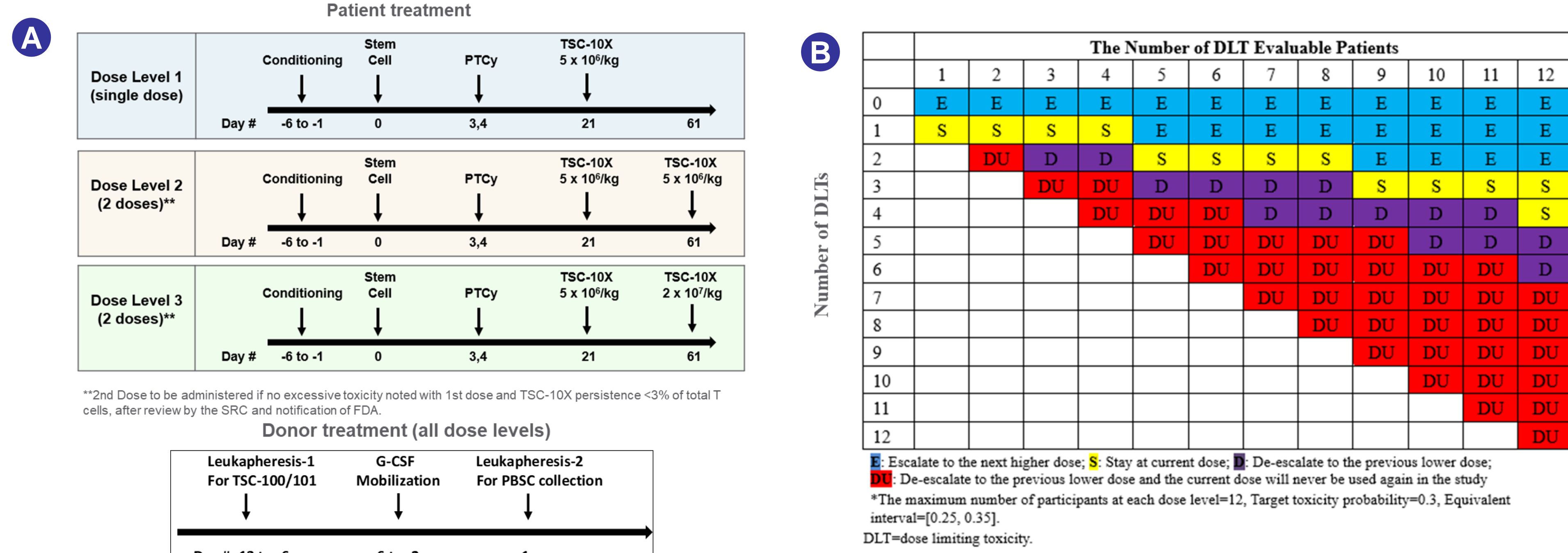
- Age ≥18 years
- AML, MDS or ALL
- Reduced intensity conditioning HCT eligible
- Haploidentical donors

Key Endpoints:

- Adverse events, DLTs
- Relapse rates, DFS, OS
- 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

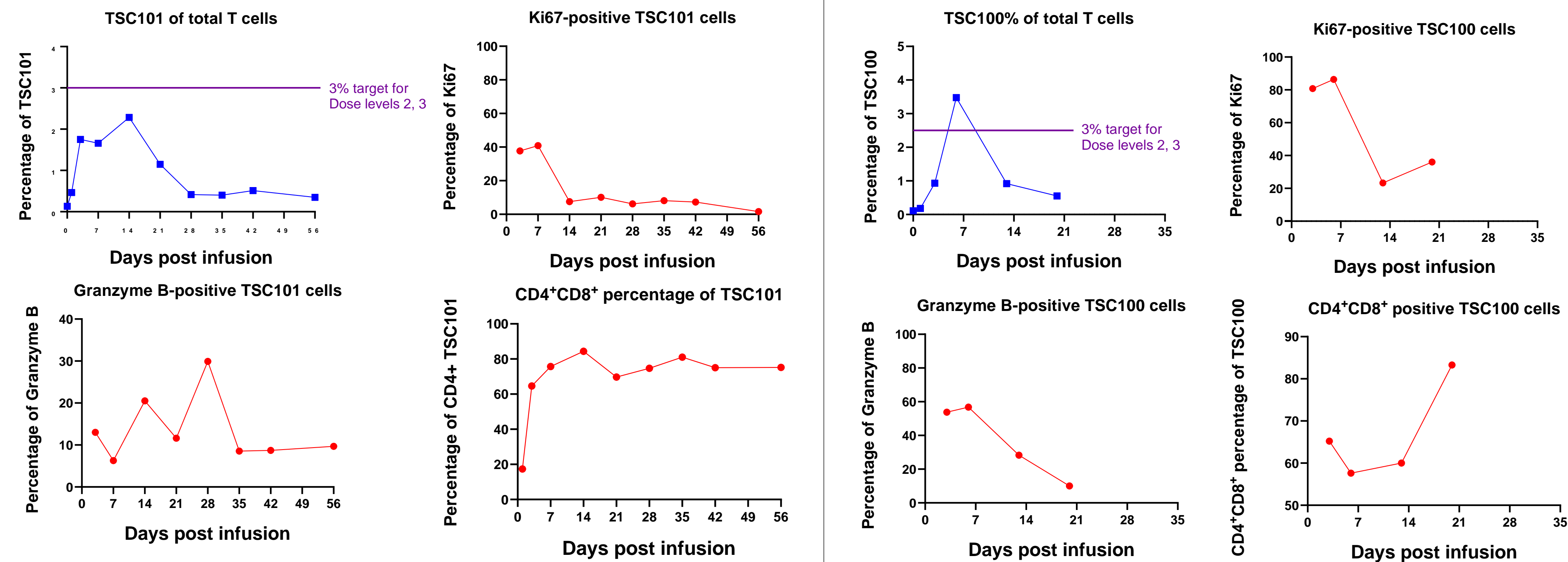
Safety Review Committee (SRC) has approved escalation to Dose Level 2 for TSC-101

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

≥Grade 2 adverse event	TSC-101/ 100 Highest grade	Control Highest grade	Arm	SAE	Grade	Days post-HCT
Diarrhea	3	2	Control	Skin GvHD	2	+49
Anemia	3	4	Control	GI GvHD	3	+53
Fatigue	2	2	Control	Pneumonia	3	+56
Thrombocytopenia	4	4	TSC-101	GI GvHD	3	+67
Vomiting	2	2				
Neutropenia	4	4				
Hypertension	2	3				
Hypomagnesemia	2	1				
Skin/GI GVHD	3	3				

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

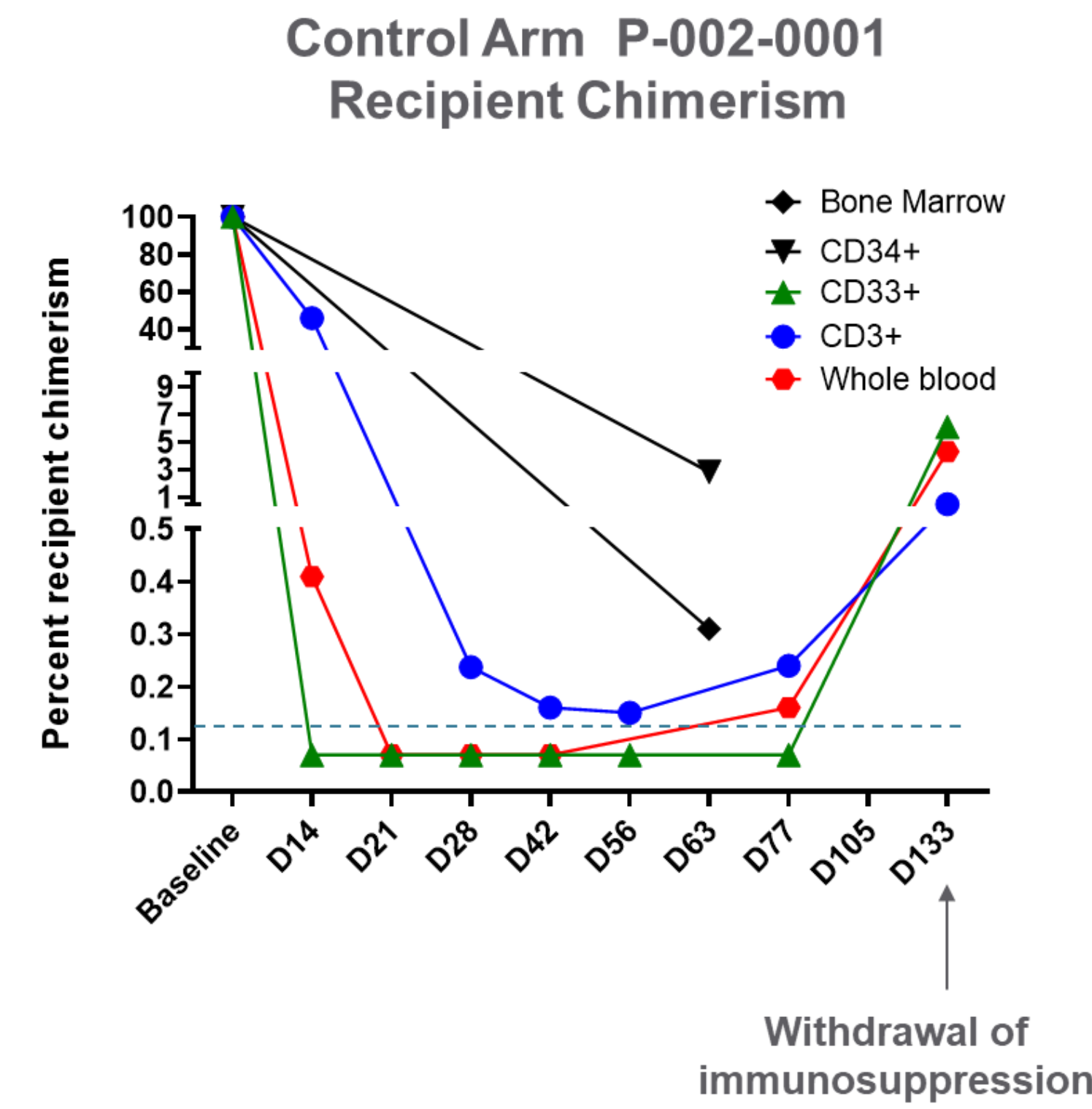
TSC-101 and TSC-100 undergo expansion, activation & persistence post-infusion



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)

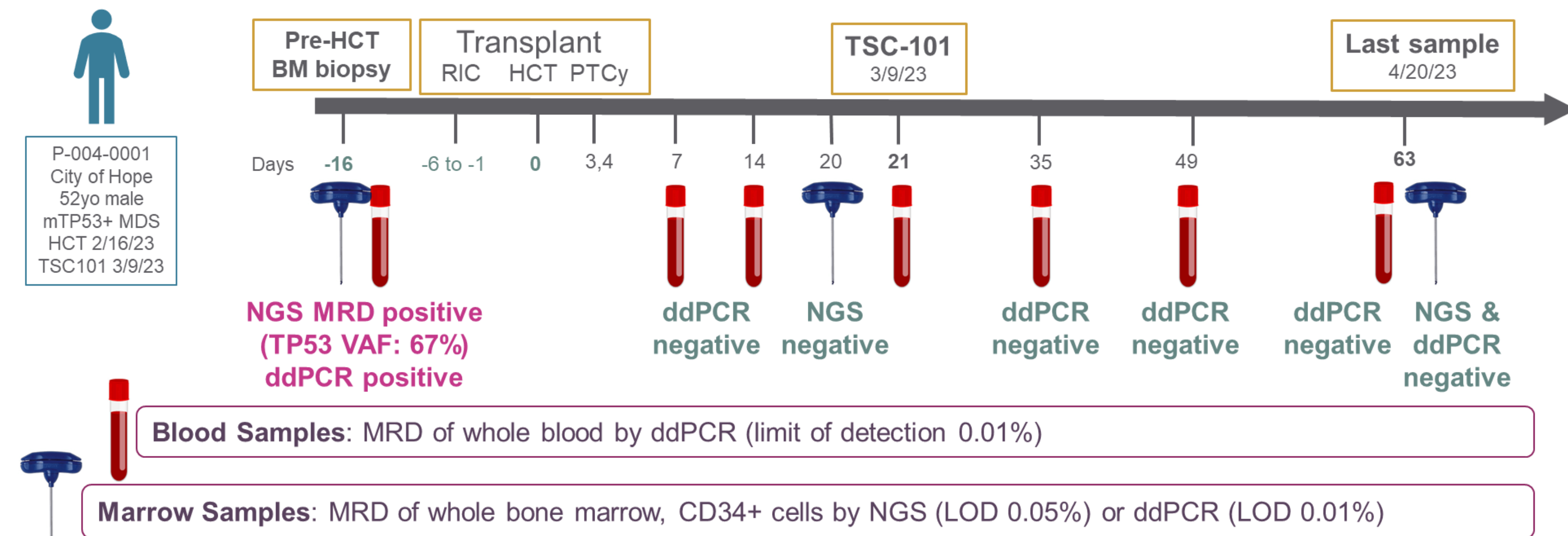
TSC-101 treated patient has undetectable recipient chimerism, unlike controls

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



UD: undetectable, D: detectable; chimerism measured with high-sensitivity Allohome 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).