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
Abstract # 798

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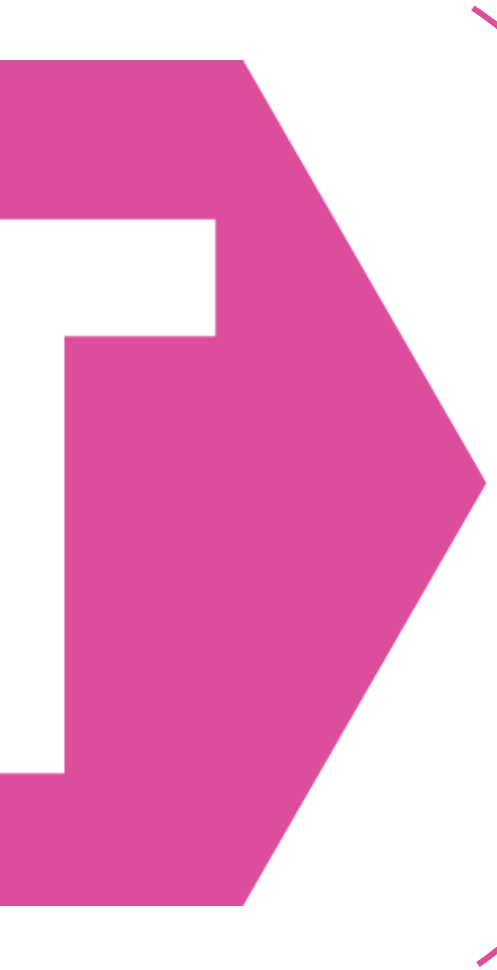
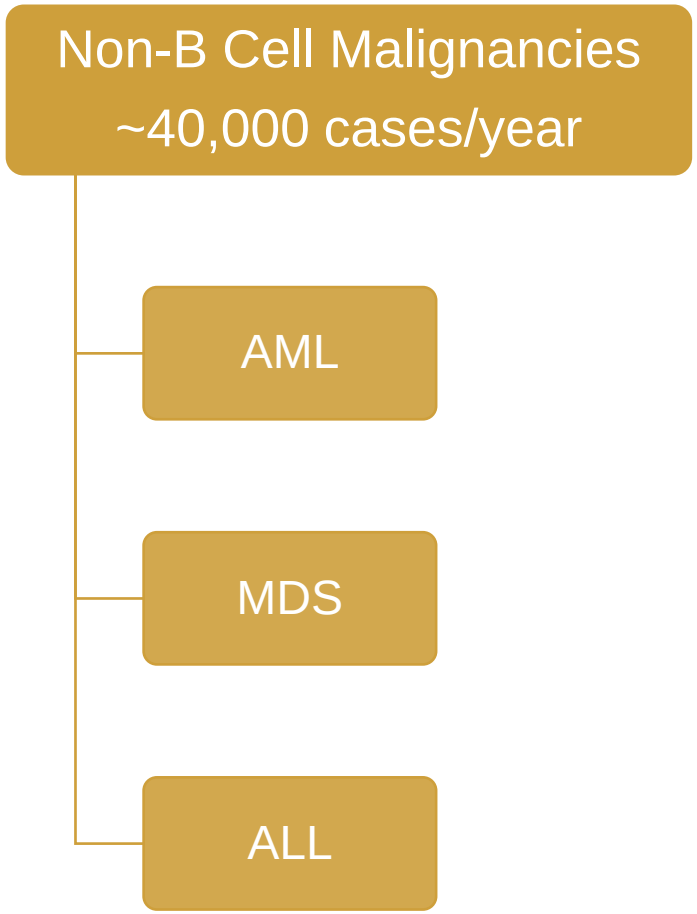
Agenda



- TSC-100/TSC-101 Study Design – Hematologic Malignancies
- Clinical and Translational Data Summary
- Case Report and KOL Discussion
- Conclusions & Summary
- Questions & Answers

Study Design

TCR-T uniquely addresses myeloid leukemias

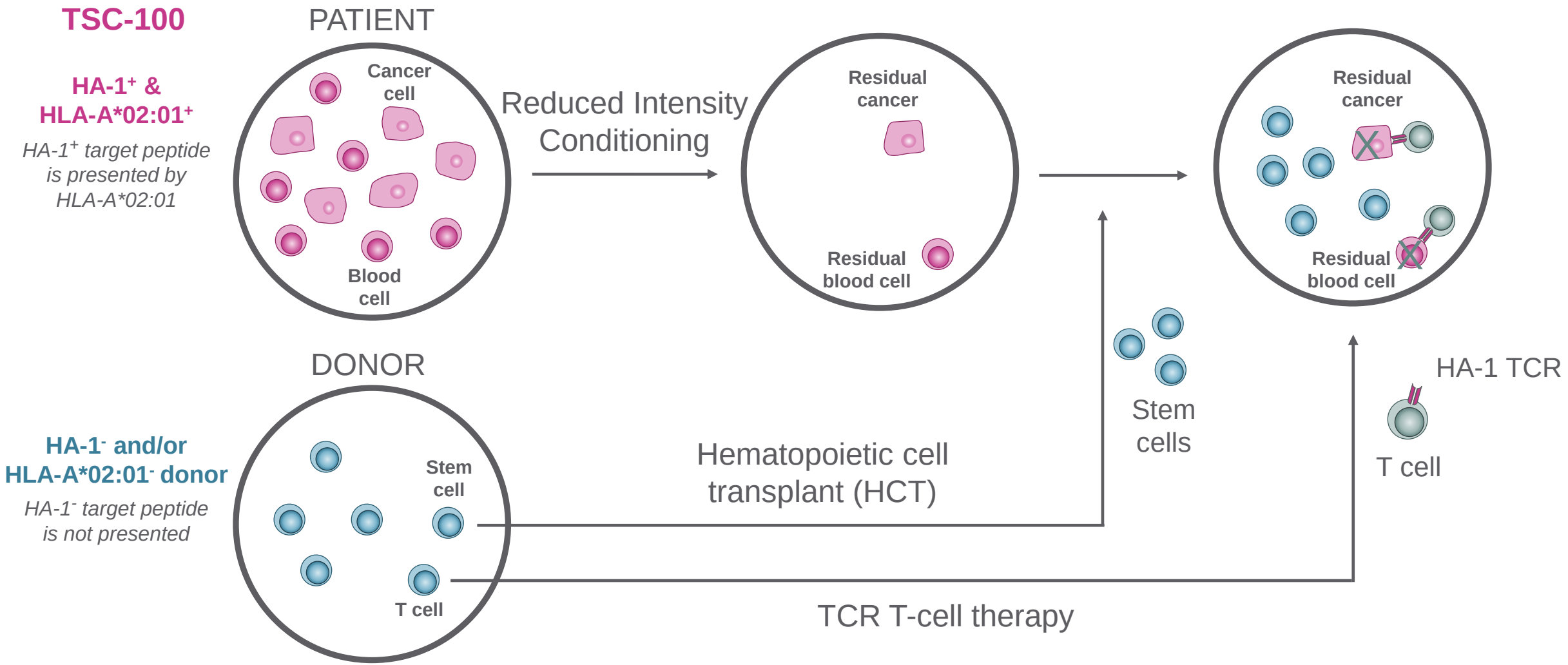


- Not addressable by CAR-T therapy
- Transplant is considered curative for many and is expected to remain standard of care
- ~40% of patients relapse post-transplant with few treatment options (~90% mortality within 1 year of relapse)

TScan program is designed to prevent relapse in patients undergoing HCT

Source: Independent KOL market research conducted June 2020.

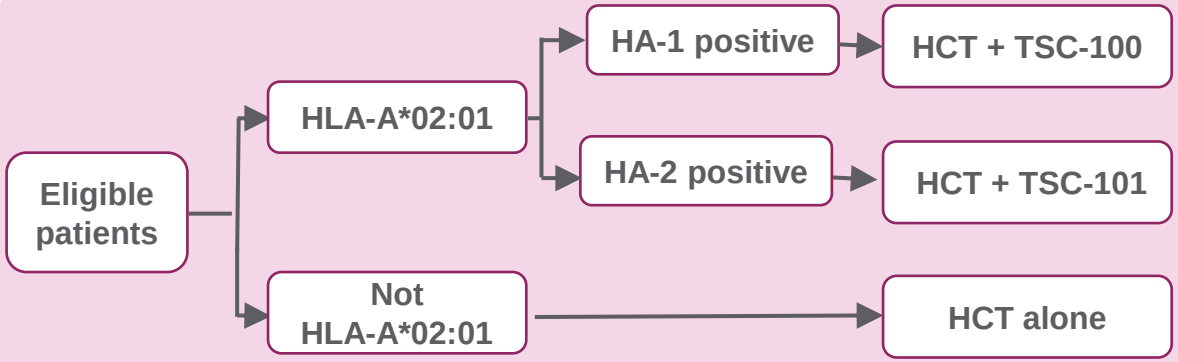
TSC-100 and TSC-101 eliminate residual leukemia after HCT by targeting patient-specific peptides on leukemia cells



TSCAN-001 Phase 1 clinical trial design for TSC-100/ TSC-101 in patients undergoing HCT

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: acute myeloid leukemia, MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; HCT: hematopoietic cell transplantation; DLTs: dose limiting toxicities; DFS: disease-free survival, OS: overall survival; MRD: minimal residual disease

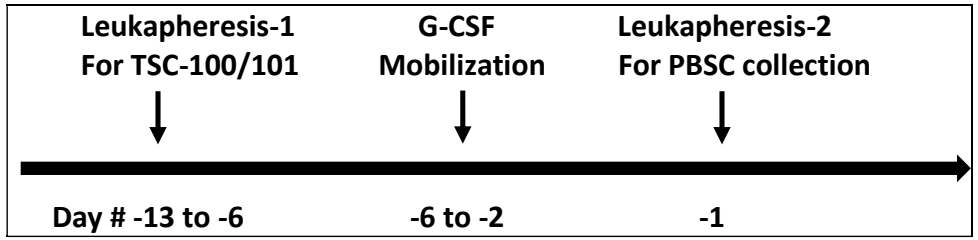
Retrospective analysis of CIBMTR data supports HLA-based assignment

1-year outcomes Percentages (CI)	Relapses	Overall survival	Acute GvHD (II-IV) at 6 months
HLA-A*02:01+ (N=444)	32 (28-37)	67 (63-72)	30 (25-34)
Not HLA-A*02:01 (N=864)	34 (30-37)	66 (63-70)	29 (26-32)

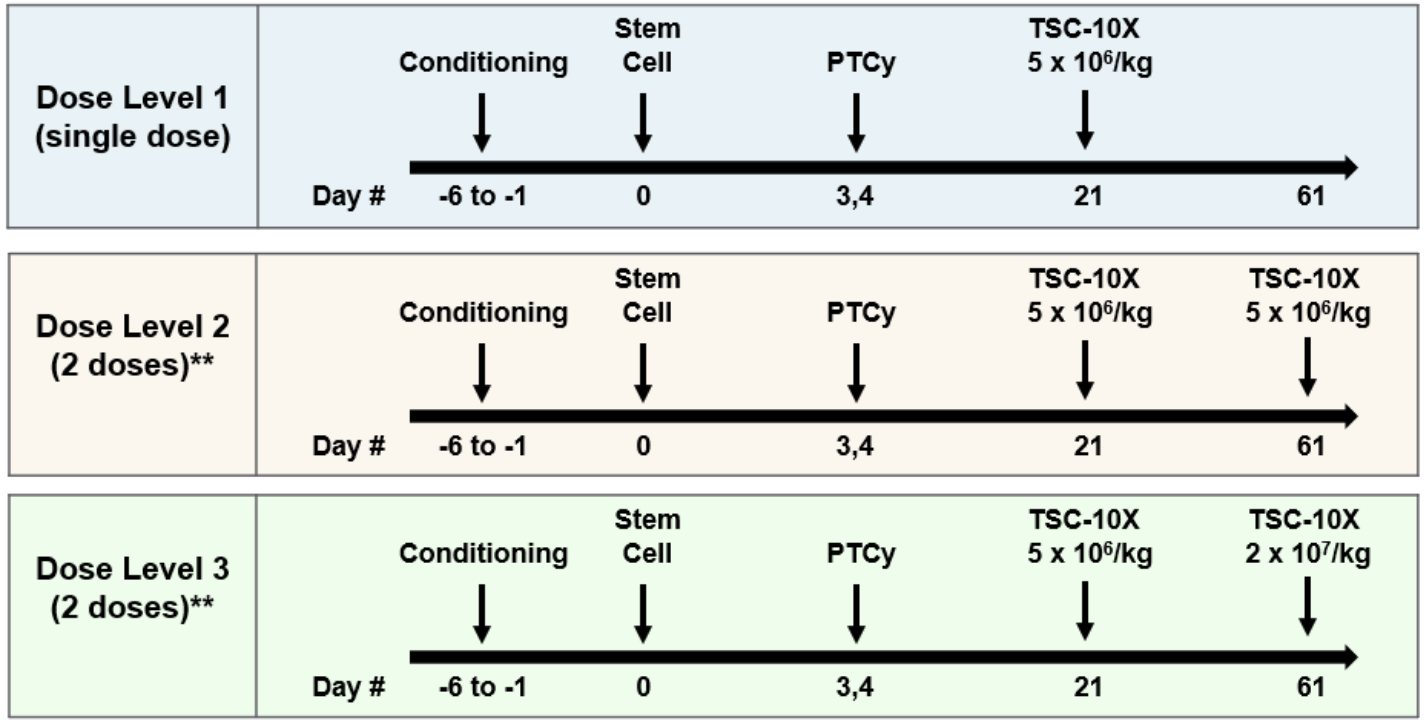
Collaborative analysis with CIBMTR of patients undergoing RIC-HCT from haploidentical donors from 2017-2019 did not find significant differences in outcomes between patients with HLA-A*02:01 and other HLA types. (CI= confidence intervals)

Dose Levels and treatment regimen for donors & patients in treatment arms

Donor treatment (all dose levels)



Patient treatment



**2nd Dose to be administered if no excessive toxicity noted with 1st dose and TSC-10X persistence <3% of total T cells, after review by the SRC and notification of FDA.

TSC-101 reached Dose Level 2 per Safety Review Committee;
TSC-100 awaiting dose escalation

i3+3 design has flexible cohort size from 1-12 participants depending on DLTs at each dose level

Number of DLTs	The Number of DLT Evaluable Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S
4				DU	DU	DU	D	D	D	D	D	S
5					DU	DU	DU	DU	DU	D	D	D
6						DU	DU	DU	DU	DU	DU	D
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E: Escalate to the next higher dose; S: Stay at current dose; D: De-escalate to the previous lower dose;
DU: De-escalate to the previous lower dose and the current dose will never be used again in the study

*The maximum number of participants at each dose level=12, Target toxicity probability=0.3, Equivalent interval=[0.25, 0.35].

DLT=dose limiting toxicity.

Differences of i3+3 design:

- Dose escalation allowed with 1 participant per dose level if no DLTs observed
- Dose level can be de-escalated if DLTs are observed
- i3+3 has flexibility of moving between dose levels unlike the standard 3+3 design

The i3+3 design for phase I clinical trials.
Liu et al, J Biopharm Stat;30:294-304 (2020)

Clinical Data Summary

Patients have been enrolled into all 3 arms of the study

	TSC-101	TSC-100	Control Arm	
Patient ID	P-004-0001	P-004-0004	P-002-0001	P-007-0001
Diagnosis	MDS with TP53 mutation	T-cell ALL	MDS	MDS
Molecular Markers	Del5q, mTP53	ATM <2%	Trisomy 8	None
Pre-HCT MRD	Positive (**TP53 67% VAF**)	Negative	Positive (**SRSF2 35% VAF**)	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 date	9 Mar 2023	19 Apr 2023	N/A	N/A

Safety: adverse events ≥Grade 2 are similar in all arms

Adverse event ≥Grade 2	TSC-100/ 101 arms Highest Grade	Control arm 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

Safety: serious adverse events (SAEs) post-HCT in all arms

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

Patient 004-0001 treated at City of Hope

52 yo Hispanic male with treatment related MDS (related to prior follicular lymphoma treatment) with 5q deletion and TP53+ mutation

MDS diagnosed: 22 Sep 2022

Prior Treatments :

- ***Follicular lymphoma***: Mosunetuzumab, MALT 1 inhibitor-copanlisib, obinutuzumab/ Revlimid, CAR T cell therapy (axi-cel)
- ***MDS***: None

Donor description:

- Age: 17
- Gender: male
- Relationship: child
- ID screening results: Neg for CMV/EBV

Medical History: follicular lymphoma, diabetes mellitus, pancytopenia, obstructive uropathy, post covid pulmonary disease, hypogammaglobulinemia

ECOG: 1 (screening period)

MRD status: MRD negative by flow cytometry at screen, MRD+ by NGS (TP53, 67% variant allelic fraction)

RIC Regimen/Date: Flu/Mel / TBI, given 11 Feb 2023

Date of Transplant: 16 Feb 2023

- Count recovery occurred on ~ 3/5/23 (Day 17)
- G-CSF was given on 3/9, 3/10, 3/11 (Days 21, 22, 23)

Date of TSC-101 treatment: 9 March 2023 (Day 21)

Dose Level: 4.3 x 10^6/ kg (target dose 5 x 10^6/ kg)
=TOTAL of 4.765 X 10^8 cells (476 million cells)

DLTs: ***None in 40-day monitoring period ending 4/18/23***

SAEs:

- Acute bronchitis hospitalization 12/27/22-01/05/23, occurred prior to transplant, delayed transplant date
- ***Hospitalization for Grade 3 gut GvHD and acute kidney injury, 47 days after TSC-101, resolved after steroids***

TSCAN THERAPEUTICS

ANC and Platelets- no count drop after TSC-101

Visit	Visit Date	ANC	Platelets
SCREENING	21-Dec-22	3.1	72
RIC Treatment (Day -6 to -1)	11-Feb-23	0.9	108
Hematopoietic cell infusion/PTCy (Day 0)	16-Feb-23	ND	38
Day 3	19-Feb-23	UNK	12
Day 4	20-Feb-23	UNK	7
Day 7	23-Feb-23	ND	10
Day 14	2-Mar-23	ND	9
Day 21 **TSC101 Treatment given	9-Mar-23	0.8	15
Day 28	16-Mar-23	2.1	21
Day 35	23-Mar-23	2.7	27
Day 42	30-Mar-23	3.4	56

No cytokine release syndrome symptoms or ferritin/ CRP increase after TSC-101 treatment

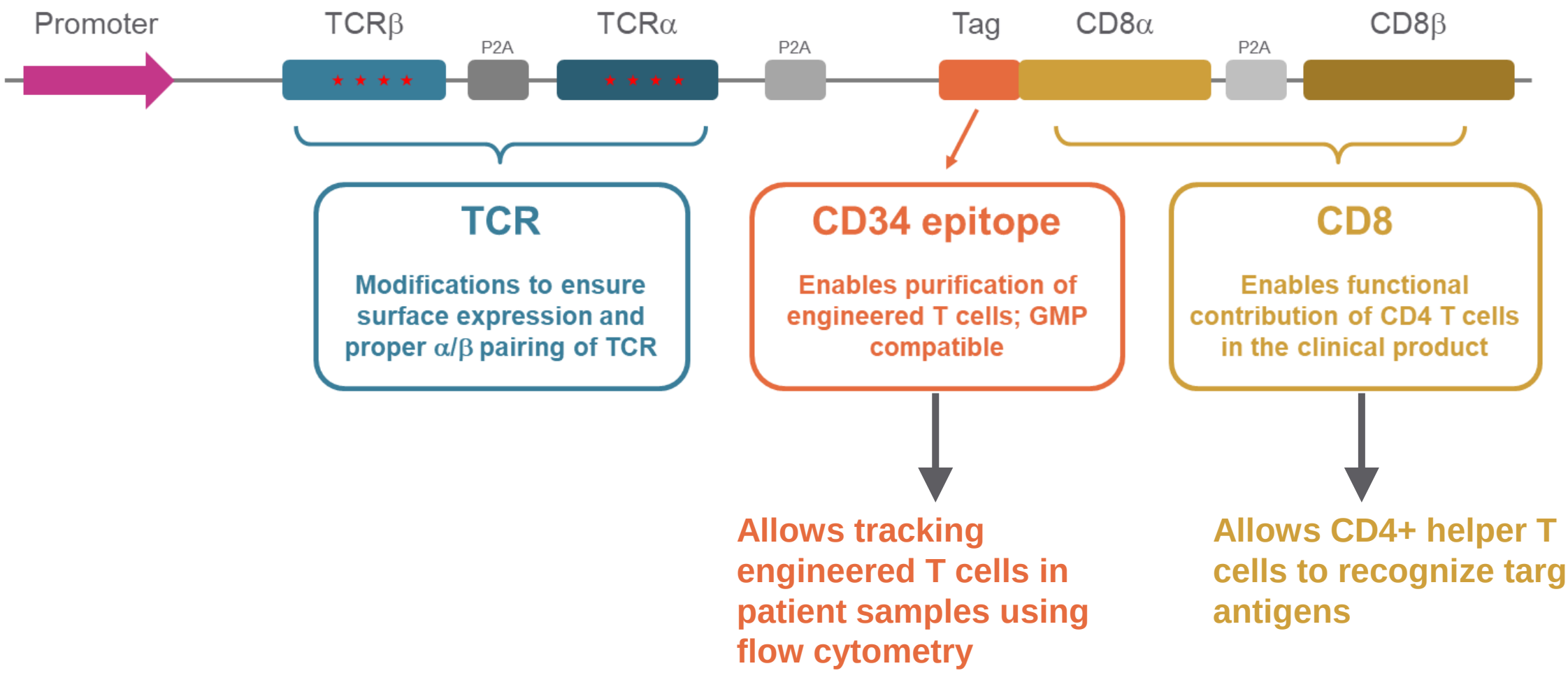
Transplant Day	Visit Date	CRP	Ferritin
Day 7	23-Feb-23	52	959.4
Day 14	2-Mar-23	233	2146
Day 21 **TSC101 Treatment **	9-Mar-23	26	1375
Day 28	16-Mar-23	5	1486
Day 42	30-Mar-23	33	990.9

C-Reactive Protein: marker of IL-6; **Ferritin**: marker of TNF-alpha

Note: CRS is rare with TCR-T treatment post-HCT (Chapuis et al, Nat Medicine 2019; 25:1064-1072)

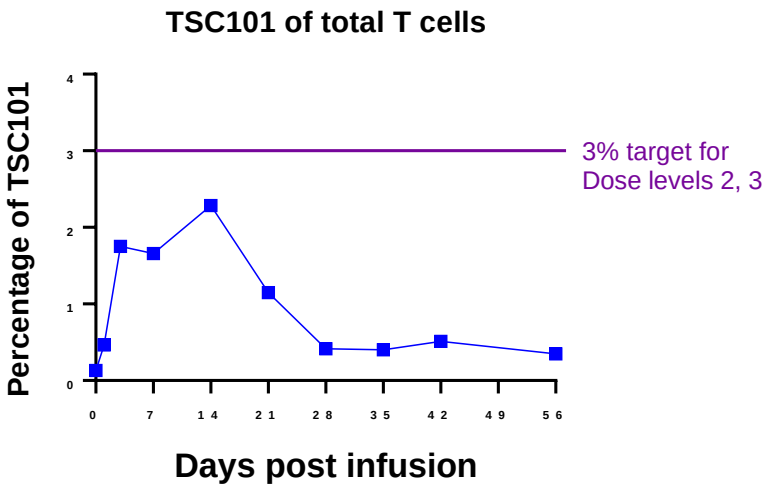
Translational Data Summary

Vector for TSC-100 and TSC-100 enables tracking engineered T cells in vivo, CD4+ T cells to recognize target antigen

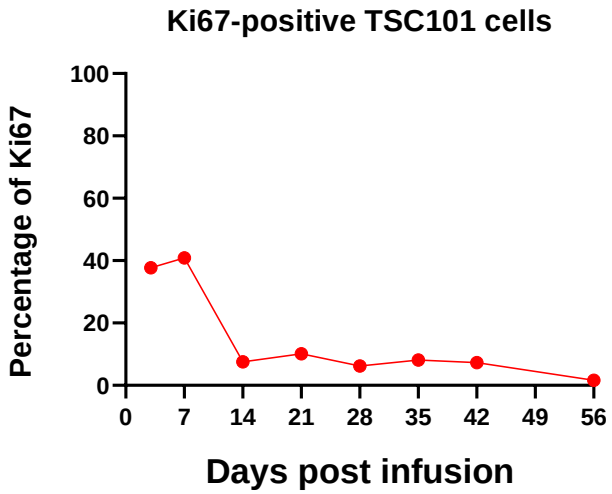


TSC-101 cells show expansion, proliferation, activation and persistence by flow cytometry

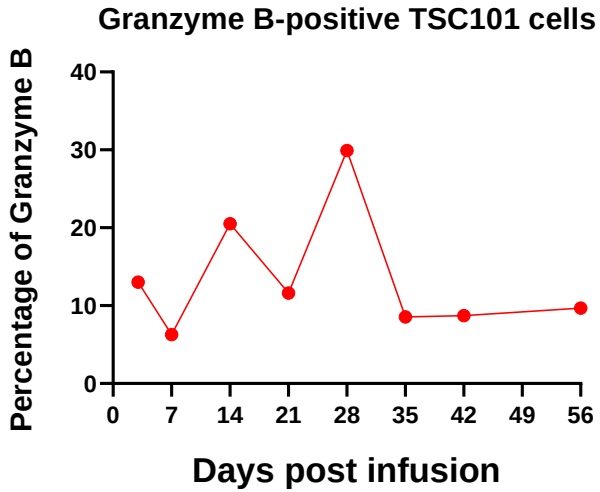
Persistence

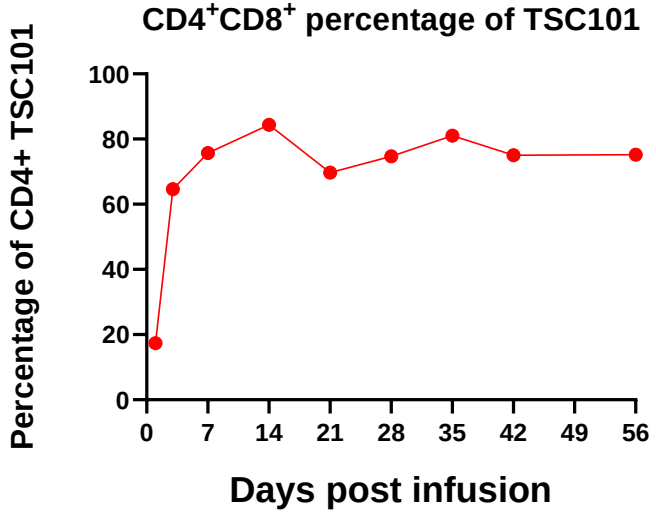


Proliferation



Activation



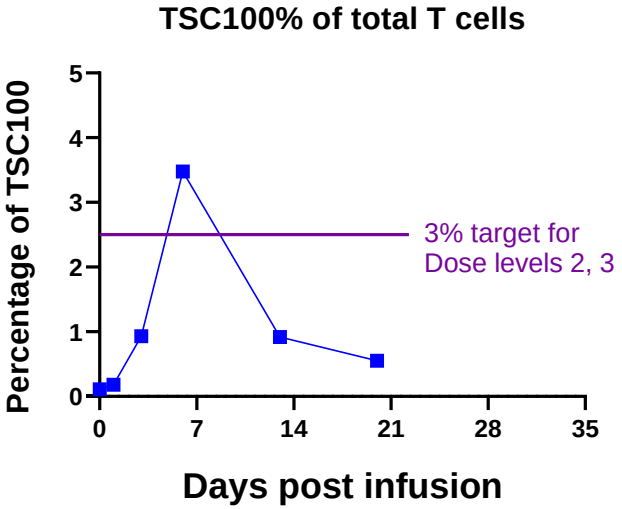


CD4+ long-term persister cells*

*Decade-long leukemia remissions with persistence of CD4+ CAR T cells. Melenhorst, Nature; 602, 503–509 (2022)

TSC-100 cells show early expansion, activation & proliferation

Persistence



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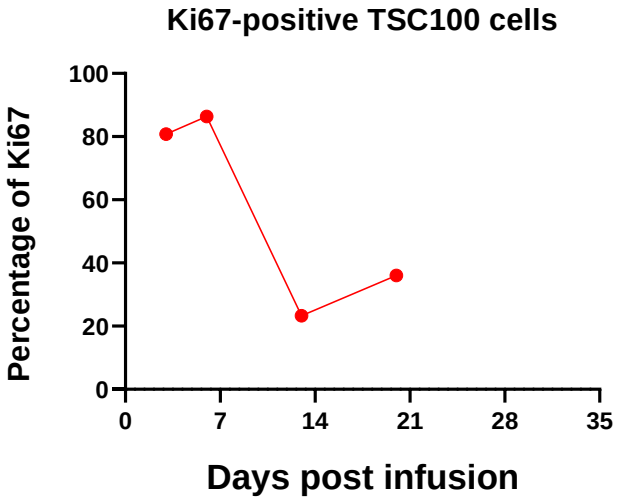

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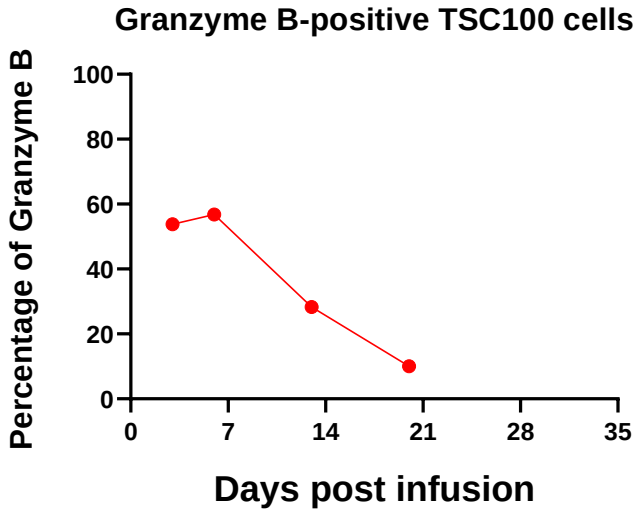
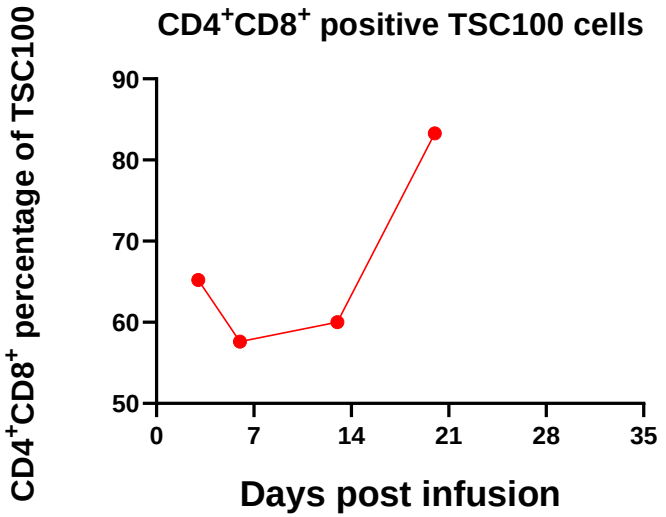




CD4+ long-term persister cells*

*Decade-long leukemia remissions with persistence of CD4+ CAR T cells. Melenhorst, Nature; 602, 503–509 (2022)

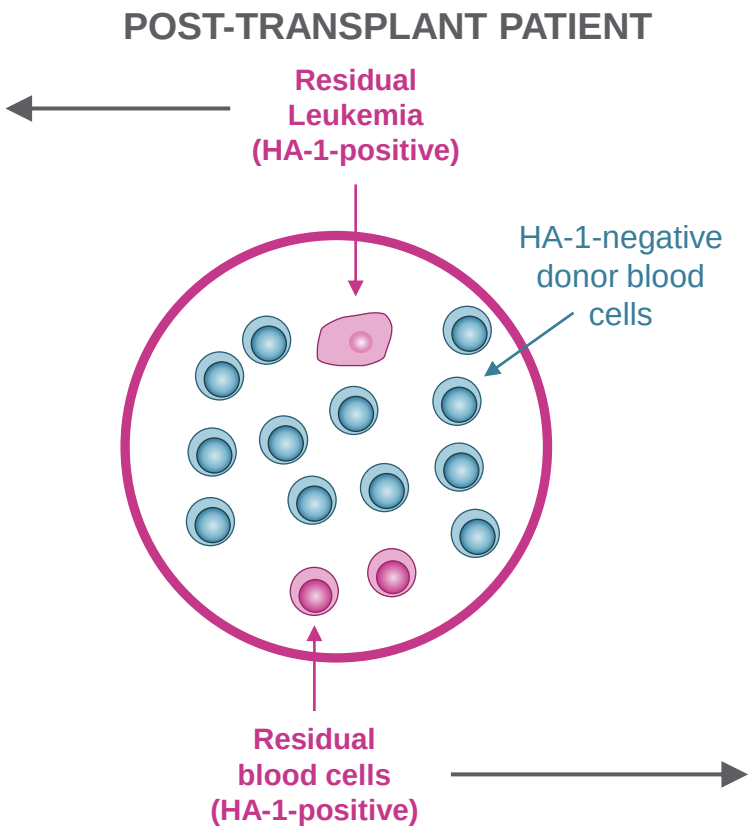
Key biomarkers measure residual leukemia or residual patient-derived blood cells as surrogates of efficacy

Minimal Residual Disease (MRD)

Conventional
- MRD by flow cytometry
- Sensitivity ~0.1%
- Performed at local sites

High sensitivity
- MRD by NGS and ddPCR
- Sensitivity ~0.01%
- Performed at Columbia University

MRD+ patients post-transplant (~30%) have ~90% chance of relapse[1,2].



Mixed donor cell chimerism

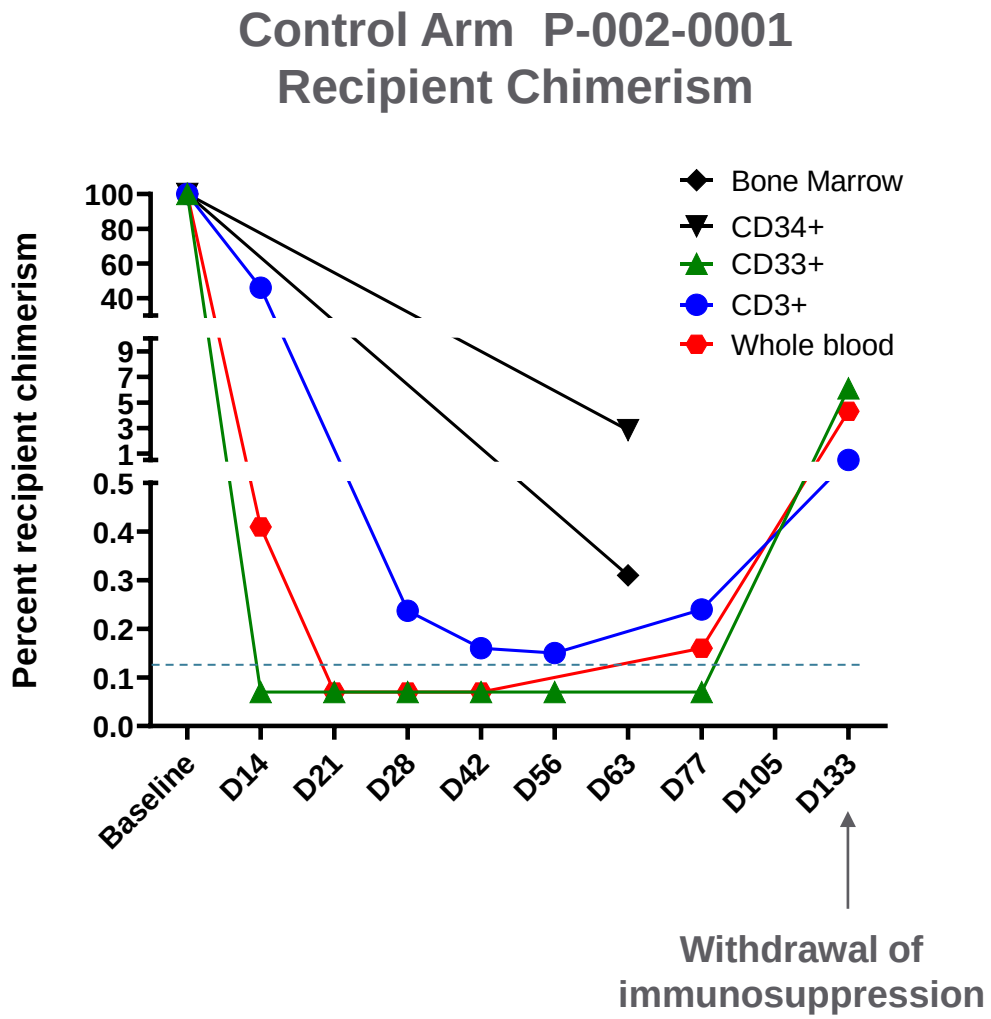
Conventional
- STR assay
- Sensitivity ~1%
- Performed at LabCorp

High sensitivity
- NGS-based Alloheme assay
- Sensitivity ~0.13%
- Performed by CareDx

1. Craddock, J Clin Oncol 2021
2. Loke, ASH 2021

TSC-101 treated patient shows undetectable patient (recipient) chimerism compared to control arm patients

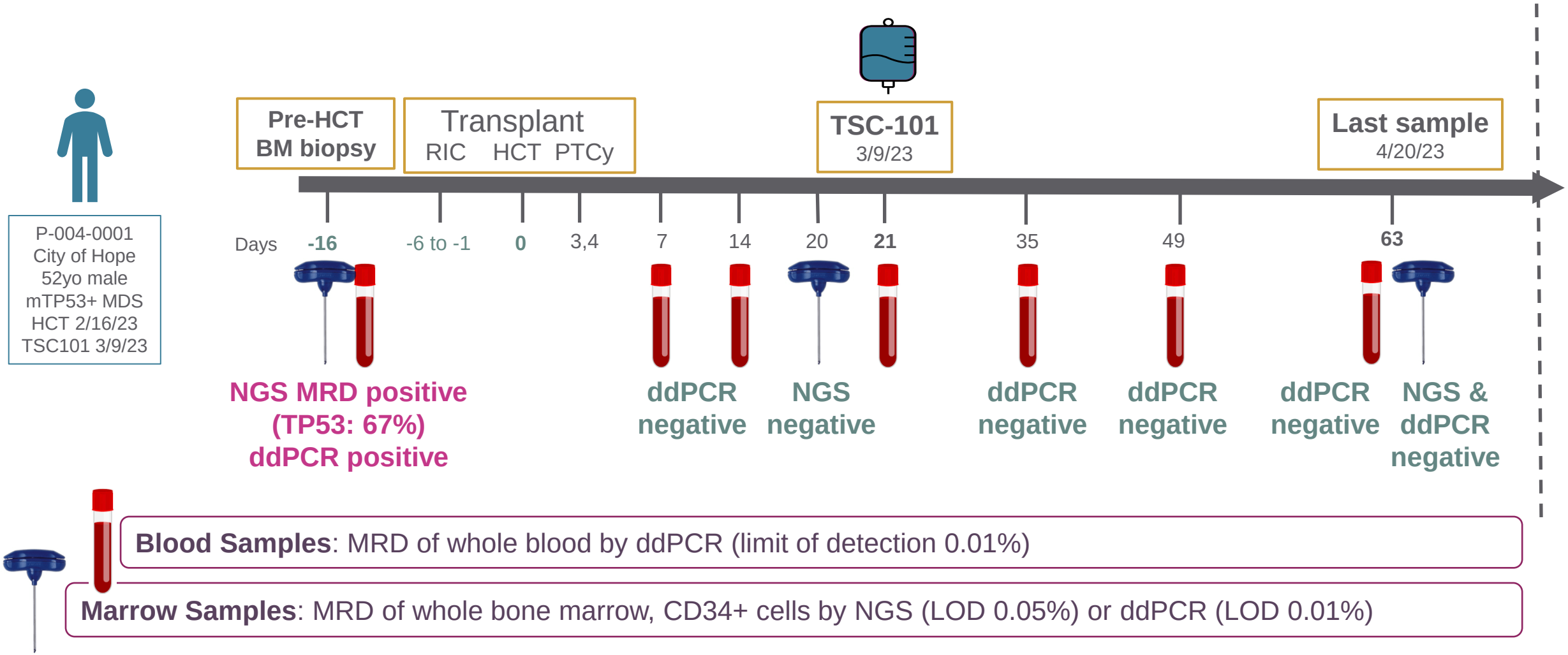
Day post HCT	Subset	P-004-0001 (TSC-101)	P-002-0001 (Control)	P-007-0001 (Control)
Day 21 (TSC-101)	CD33 CD3 Whole blood	UD D D	UD D UD	D D D
Day 35	CD33 CD3 Whole blood	UD D D	UD D UD	D UD D
Day 42	CD33 CD3 Whole blood	UD UD UD	UD D UD	D D D
Day 56	CD33 CD3 Whole blood	UD UD UD	UD D UD	D UD D
Day 63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



UD: undetectable, D: detectable

Recipient chimerism detected by high-sensitivity NGS-assay (Alloheme) with LOD 0.13%

TP53 mutant MDS patient turned from MRD positive pre-HCT to MRD negative post-HCT and TSC-101 treatment

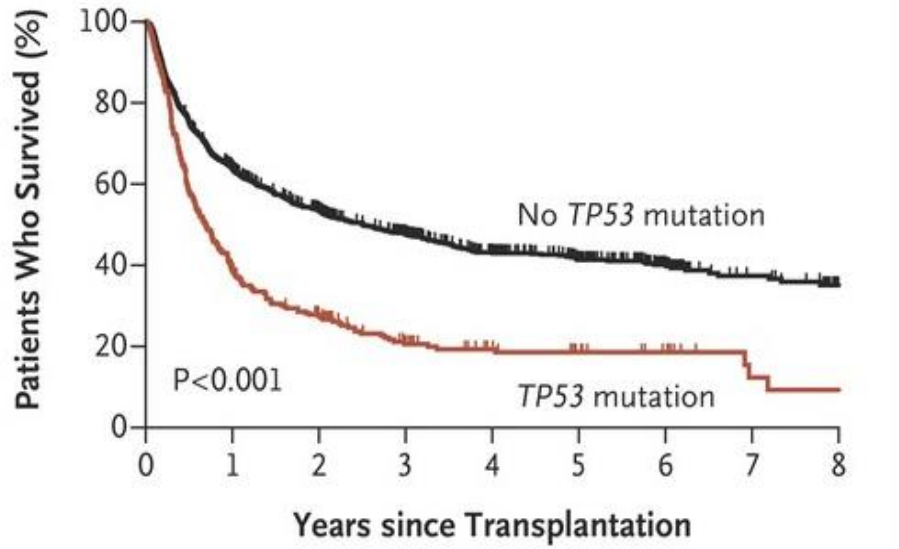


Blood Samples: MRD of whole blood by ddPCR (limit of detection 0.01%)

Marrow Samples: MRD of whole bone marrow, CD34+ cells by NGS (LOD 0.05%) or ddPCR (LOD 0.01%)

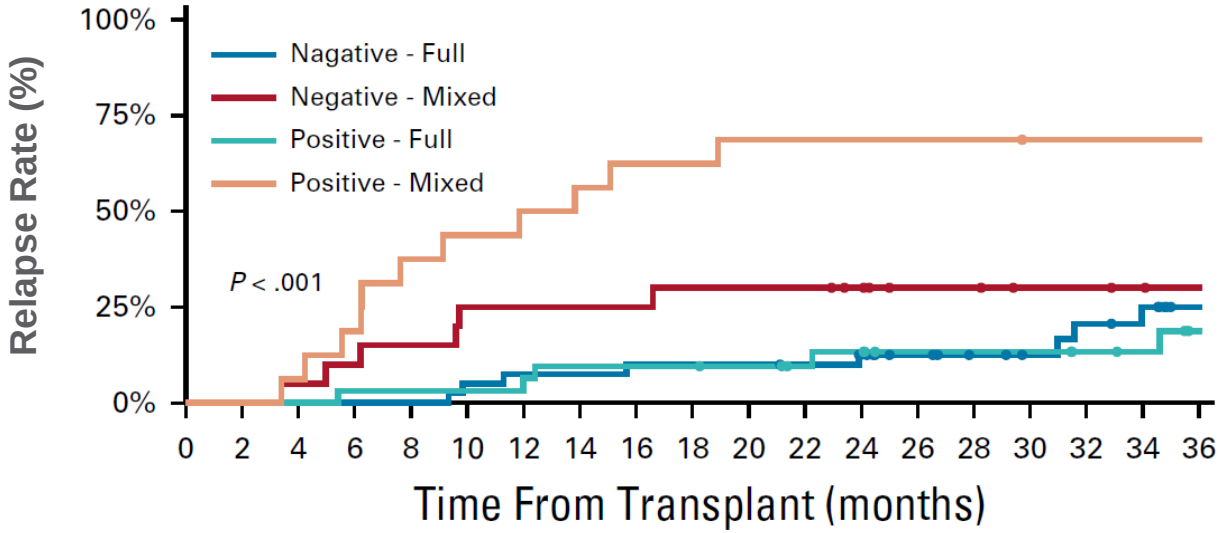
Achieving MRD negativity and full donor chimerism post-HCT is generally meaningful, particularly in TP53 mutant patients

TP53 mutant MDS patients have >80% risk of relapse/ death after HCT



Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation
Lindsley RC et al., N Engl J Med 2017;376:536-547.

MRD negativity with full donor chimerism post-HCT associate with low risk of relapse for AML



Caveats:
1. AML patients treated with different RIC regimen (FLAMSA-Bu)
2. MRD measured at Day 42 by flow alone (16% positivity post-HCT)
3. Chimerism measured around Day 90 in CD3+ subset alone

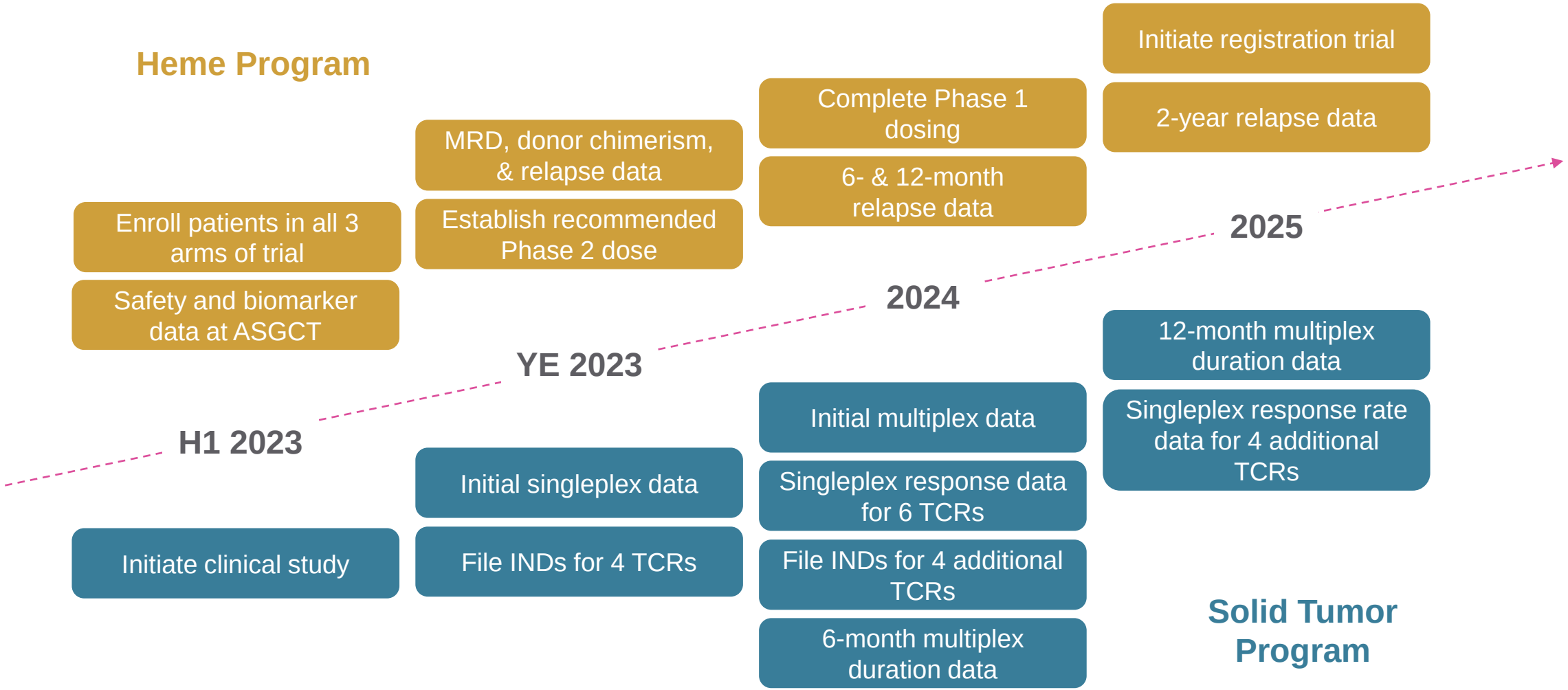
Craddock C et al., J Clin Oncol 2021; 39:768-778.

Conclusions & Summary

Summary of clinical and translational data

- Four patients enrolled: one in TSC-101 arm, one in TSC-100 arm, two in control arm
- No safety concerns noted with TSC-101 or TSC-100 to date
- Safety Review Committee approved escalation to dose level 2 for TSC-101
- Peripheral blood sampling reveals expansion, proliferation, activation and persistence of TSC-101 and TSC-100
- Recipient chimerism is undetectable in TSC-101 treated patient compared with 2 control arm patients using high-sensitivity NGS method
- TP53 mutant MDS patient turned from MRD+ pre-HCT to MRD negative post-HCT and TSC-101 treatment using high-sensitivity NGS/ ddPCR methods

Steady value-generating data flow across clinical programs



Questions and Answers