Initial Results of a Phase 1 trial of TSC-100 and TSC-101, Engineered T Cell Therapies that Target Minor Histocompatibility Antigens to Prevent Relapse after Allogeneic Hematopoietic Cell Transplantation

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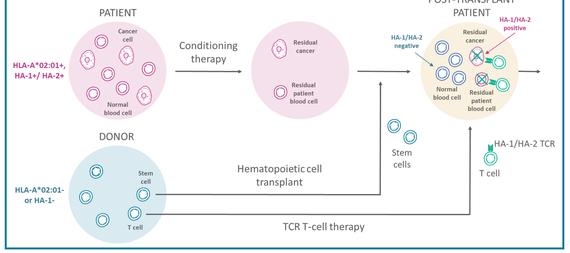
Abstract # 2090

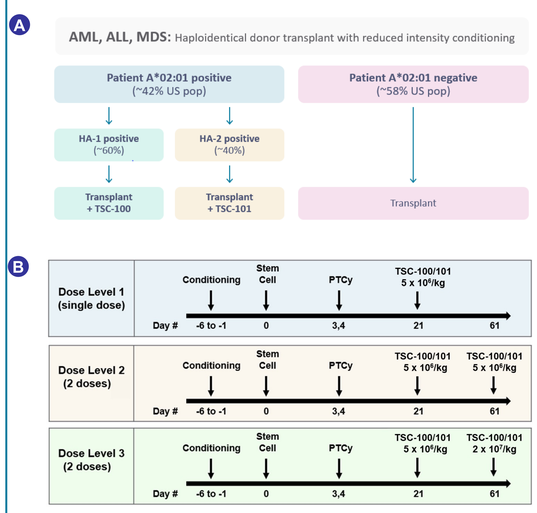
Study Design

Background and rationale

- Allogeneic hematopoietic cell transplantation (HCT) remains the best curative option for most hematologic malignancies, yet relapses occur in ~40% of patients post-HCT and are associated with high mortality.
- A potential solution is targeting hematopoietic lineage-specific minor histocompatibility antigens mismatched between transplant recipients and their donors.
- TScan has developed the engineered T cell products TSC-100 and TSC-101 that express TCRs targeting MiHAs HA-1 and HA-2 respectively, both presented by HLA-A*02:01 and expressed only in hematologic cells.
- By choosing HCT patients who are HLA-A*02:01 positive and either HA-1 or HA-2 positive, and donors who are mismatched on either MiHA or HLA-A*02:01, TSC-100 and TSC-101 are designed to eliminate all residual recipient hematologic cells while leaving donor hematologic cells untouched.



Treatment based on HLA & HA-1/HA-2 status



A. Treatment assignment scheme. **B**. Dose levels for TSC-100/101

TSC-100 and TSC-101 are well tolerated

Patients enrolled at all three dose levels; no DLTs observed to date

	TSC-100				TSC-101				Control Arm			
Patient ID	P-004-0004	P-007-0002	P-004-0007	P-006-0003	P-004-0001	P-004-0005	P-004-0006	P-004-0008	P-002-0001	P-007-0001	P-006-0001	P-006-0002
Diagnosis	T-ALL	AML	AML	MDS	MDS	AML	B-ALL	B-ALL	MDS	MDS	MDS	AML
Molecular Markers	ATM <2%	FLT3-ITD	Trisomy 8 IDH2, NRAS, ASXL1	SRSF2 ASXL1 STAG2	Del5q, mTP53	IDH2, SRSF2, ASXL1 CUX1	n/a	n/a	Trisomy 8, SRSF2 ASXL1	None	Del5q Mono 7 mTP53	Mono 7, RUNX1, EZH2
Pre-HCT MRD	**Positive**	Negative	**Positive**	**Positive**	**Positive**	**Positive**	Negative	Pending	**Positive**	Negative	**Positive**	Pending
RIC regimen	Flu/ Cy/ TBI	Thio/ Bu/ Flu	Flu/Mel/ TBI	Flu/Cy/ TBI	Flu/ Mel/ TBI	Flu/Mel/ TBI	Flu/Mel/ TBI	Flu/Mel/ TBI	Flu/ Cy/ TBI	Flu/ Cy/ TBI	Flu/Mel/ Thio	Flu/ Cy/ TBI
HCT date	21 Mar 2023	27 Apr 2023	08 Sep 2023	31 Oct 2023	16 Feb 2023	20 Apr 2023	22 Jun 2023	05 Oct 2023	01 Nov 2022	03 Feb 2023	25 May 2023	29 Aug 2023
Dose Level	DL1	DL2	DL3	DL3	DL1	sDL2#	DL2	sDL3#	N/A			
TCR-T treatment day	#1 Day 29	#1 Day 25 #2 Day 76	#1 Day 34 #2 Day 75	#1 Day 27 *#2 Day 69**	#1 Day 21	#1 Day 27 #2 Day 82	#1 Day 21 #2 Day 62	#1 Day 27 *#2 Day 70**	N/A			

Dose did not meet target dose criteria, * scheduled dosing

Most frequent and serious adverse events similar in treatment and control arms

A

Adverse event ≥Grade 2	TSC-100/ 101 arms Highest Grade# N=8	Control arm Highest Grade# N=4
Anemia	3	4
Abdominal Pain	2	2
Nausea/ vomiting	2	2
Diarrhea	3	2
Fatigue	2	2
Pyrexia	2	3
Pneumonia	2	3
ALT/ AST increased	3	2
Thrombocytopenia	4	4
Neutropenia	3	3
Creatinine increased	2	2

Grading by CTCAE v 5.0

B

Arm	Patient ID	Serious Adverse Event	Highest Grade*	Post Transplant Day	TSC Relatedness
TSC-100-DL3	P-004-0007	Sepsis, respiratory failure	4	+9	Not applicable (pre-TSC)
TSC-101-DL2supp	P-004-0005	Pyrexia	1	+21	Not applicable (pre-TSC)
TSC-101-DL1	P-004-0001	Acute graft versus host disease in gastrointestinal tract, acute kidney injury	3	+49	Possibly related
TSC-101-DL1	P-004-0001	Adenovirus viremia, Pneumonia, Clostridium difficile infection	2	+71	Not Related
TSC-101-DL1	P-004-0001	Pyrexia	1	+148	Not Related
TSC-101-DL1	P-004-0001	Interstitial pneumonitis	2	+182	Not Related
Control Arm	P-006-0001	Cytokine release syndrome	2	+2	Not Applicable
Control Arm	P-006-0002	Neck pain	3	+53	Not Applicable
Control Arm	P-007-0001	Acute graft versus host disease in skin	3	+49	Not Applicable
Control Arm	P-007-0001	Acute graft versus host disease in gastrointestinal tract	3	+53	Not Applicable
Control Arm	P-007-0001	Pneumonia	3	+56	Not Applicable

*Grading by CTCAE v5.0 or MAGIC consortium grading for GvHD or ASTCT grading for CRS
All serious adverse events have resolved

A. Most frequent adverse events of ≥ grade 2 after Day 21 or after TSC-100/101 treatment. **B**. Serious adverse events reported after transplant in each arm. Median post-transplant follow-up in TSC-100/101 arms was 193 days (34-291 days) and in the control arm was 249 days (97-398 days).

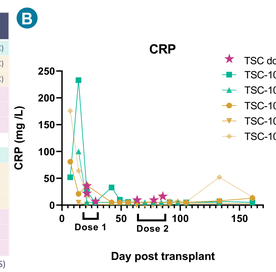
Adverse events of special interest (CRS and GvHD) similar in TSC and control arms

A

Arm-Dose Level	Patient ID	Grade*	Adverse Event	Transplant Day of Onset	Duration	TSC relatedness
TSC-100-DL2	P-007-0002	Grade 1	CRS	+3	2 days	Not applicable (pre-TSC)
TSC-101- DL2supp	P-004-0005	Grade 2	CRS	+1	3 days	Not applicable (pre-TSC)
TSC-101-DL2	P-004-0006	Grade 1	CRS	+1	5 days	Not applicable (pre-TSC)
Control	P-002-0001	Grade 1	CRS	+2	3 days	Not applicable
Control	P-007-0001	Grade 1	CRS	+3	2 days	Not applicable
Control	P-006-0001	Grade 2	CRS	+2	2 days	Not applicable
TSC-100-DL1	P-004-0004	Grade 1	Skin GVHD	+48	8 days	Possibly related
TSC-101-DL1	P-004-0001	Grade 3	GI GVHD	+49	8 days	Possibly related
TSC-101-DL2supp	P-004-0005	Grade 1	Skin GVHD	+43	3 days	Possibly related
TSC-101-DL2	P-004-0006	Grade 1	Skin GVHD	+127	7 days	Possibly related
Control	P-007-0001	Grade 3	GI GVHD	+53	18 days	Not applicable
Control	P-007-0001	Grade 3	Skin GVHD	+49	12 days	Not applicable
Control	P-002-0001	Grade 1	Skin GVHD	+180	pending	Not applicable

*MAGIC consortium grading for graft-versus host disease (GvHD); ASTCT grading for cytokine release syndrome (CRS)
All cytokine release syndrome events occurred before TSC-100/ TSC-101 treatment

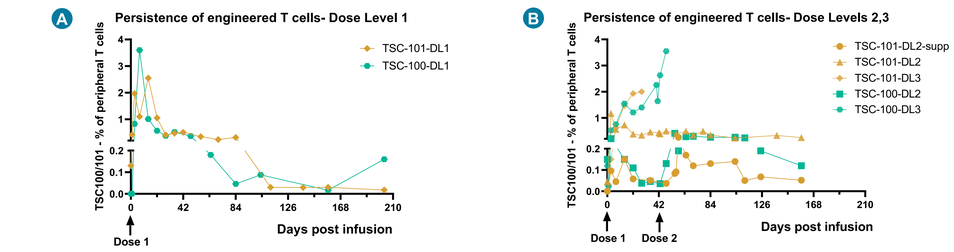
B



A. Cytokine release syndrome (CRS) and graft-versus host disease (GvHD) in all arms. **B**. No cytokine release syndrome or neurotoxicity was observed after TSC-100/101 treatment and minimal changes in CRP (laboratory marker of CRS) were observed consistent with the general safety of TSC-100/101.

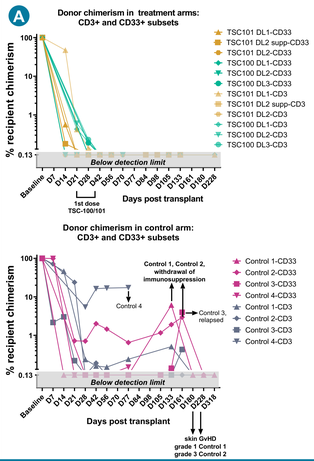
Complete donor chimerism in 6/6 (100%) treated patients versus 0/4 (0%) control patients; one relapse observed in control arm

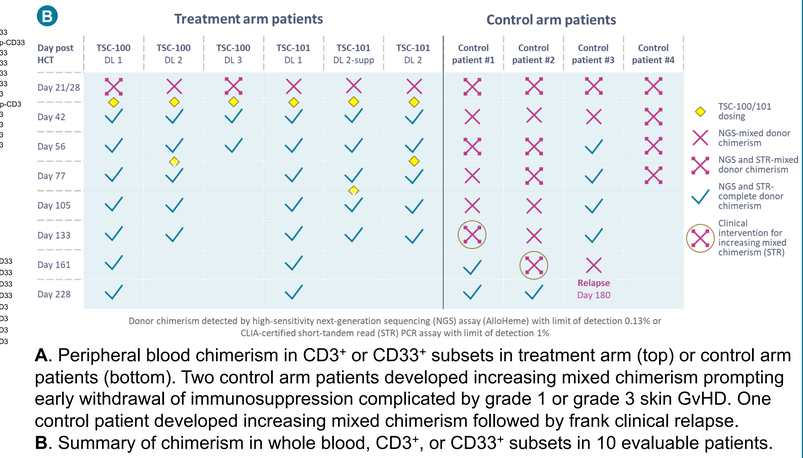
TSC-100 & TSC-101 persist in peripheral blood for over 200 days; repeat dosing results in increased levels



Persistence of TSC-100/101 in the peripheral blood measured by flow cytometry after single (**A**) or repeat dosing (**B**).

Complete chimerism in all 6 treated patients; mixed chimerism in all 4 control patients with one relapse

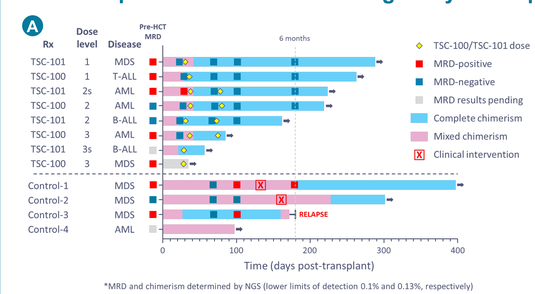


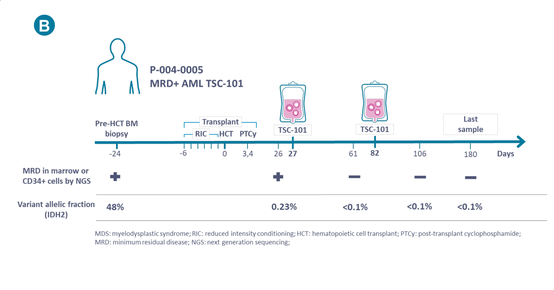


Donor chimerism detected by high-sensitivity next-generation sequencing (NGS) assay (AlloHeme) with limit of detection 0.13% or CLIA-certified short-tandem read (STR) PCR assay with limit of detection 1%

A. Peripheral blood chimerism in CD3⁺ or CD33⁺ subsets in treatment arm (top) or control arm patients (bottom). Two control arm patients developed increasing mixed chimerism prompting early withdrawal of immunosuppression complicated by grade 1 or grade 3 skin GvHD. One control patient developed increasing mixed chimerism followed by frank clinical relapse.
B. Summary of chimerism in whole blood, CD3⁺, or CD33⁺ subsets in 10 evaluable patients.

All treated patients achieved MRD negativity & complete chimerism; MRD+ to MRD- conversion observed





*MRD and chimerism determined by NGS (lower limits of detection 0.1% and 0.13%, respectively)

MDS: myelodysplastic syndrome; RIC: reduced intensity conditioning; HCT: hematopoietic cell transplant; PTCy: post-transplant cyclophosphamide; MRD: minimum residual disease; NGS: next generation sequencing;

A. Summary of MRD by next-generation sequencing (limit of detection 0.05-0.1%) and chimerism (limit of detection 0.13%) before and after hematopoietic cell transplantation (HCT). **B**. Conversion of MRD+ disease post-HCT to MRD- observed in an AML patient.