FIG. 1

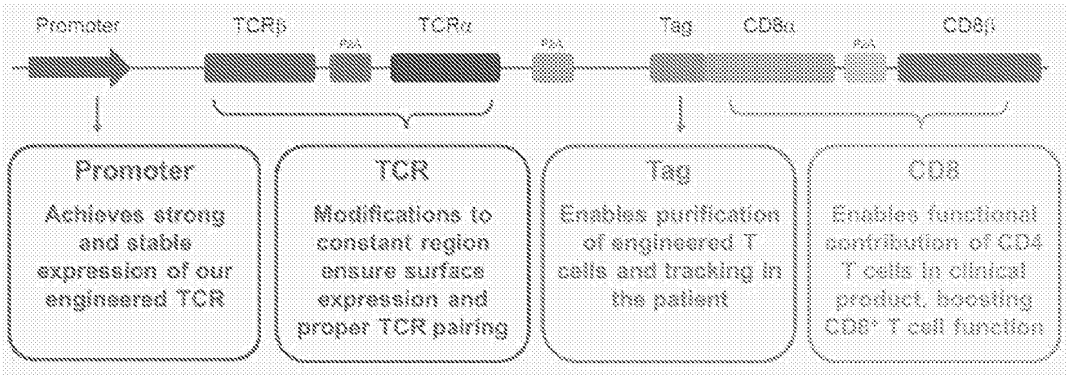
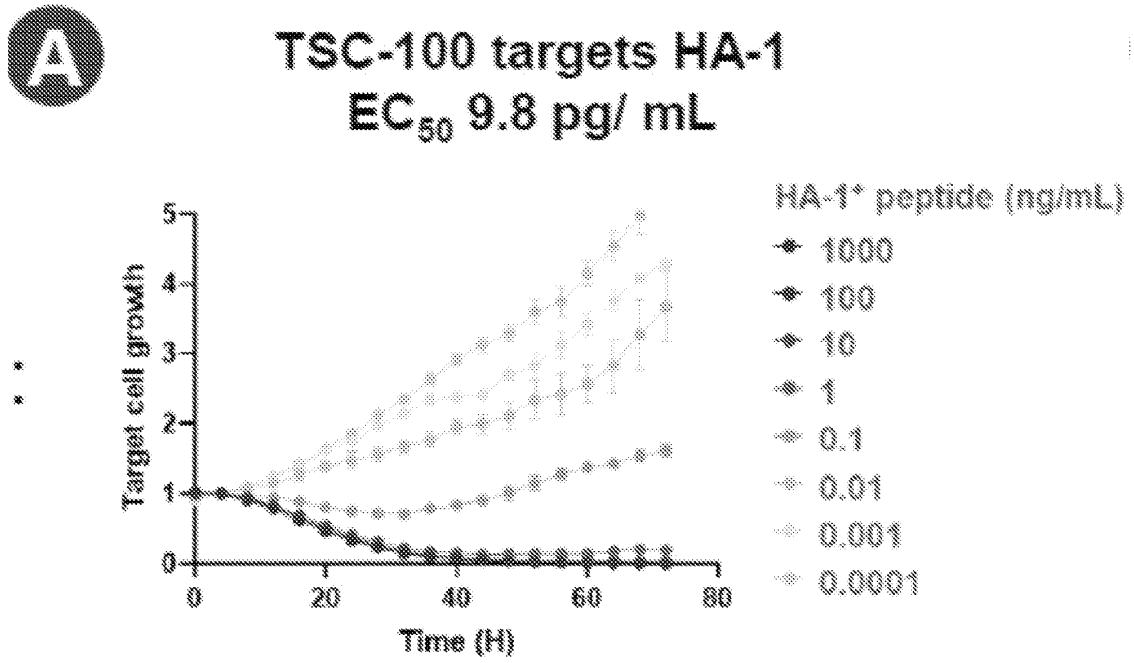

Promoter
TCRβ
P2A
TCRα
P2A
Tag
CD8α
P2A
CD8β
Promoter
Achieves strong and stable expression of our engineered TCR
TCR
Modifications to constant region ensure surface expression and proper TCR pairing
Tag
Enables purification of engineered T cells and tracking in the patient
CD8
Enables functional contribution of CD4 T cells in clinical product, boosting CD8+ T cell function

FIG. 2


A
TSC-100 targets HA-1
EC50 9.8 pg/ mL
Target cell growth
Time (H)
HA-1* peptide (ng/mL)
1000
100
10
1
0.1
0.01
0.001
0.0001

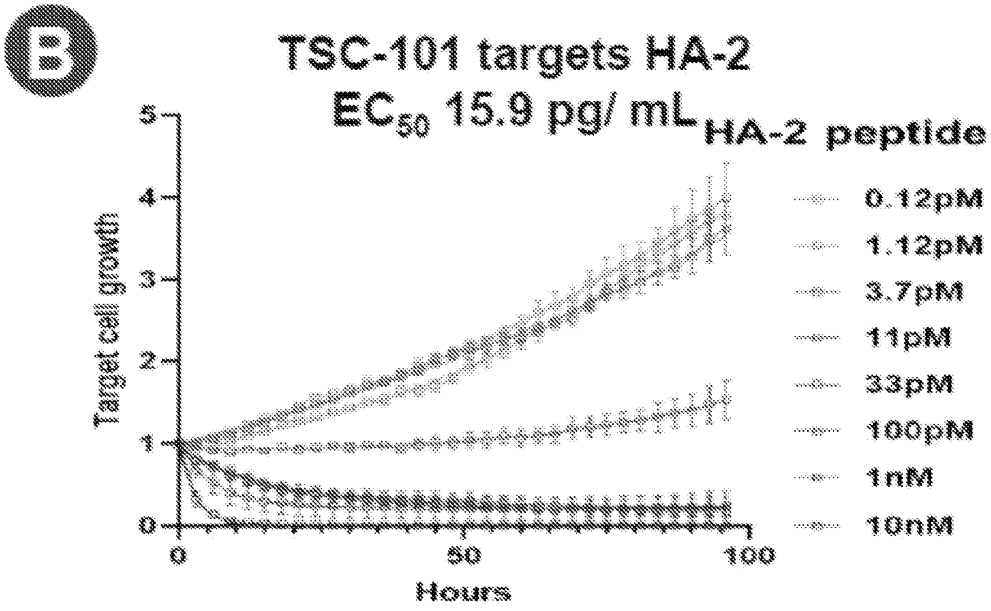

B
TSC-101 targets HA-2
EC50 15.9 pg/ mL
HA-2 peptide
Target cell growth
Hours
0.12pM
1.12pM
3.7pM
11pM
33pM
100pM
1nM
10nM

FIG. 3

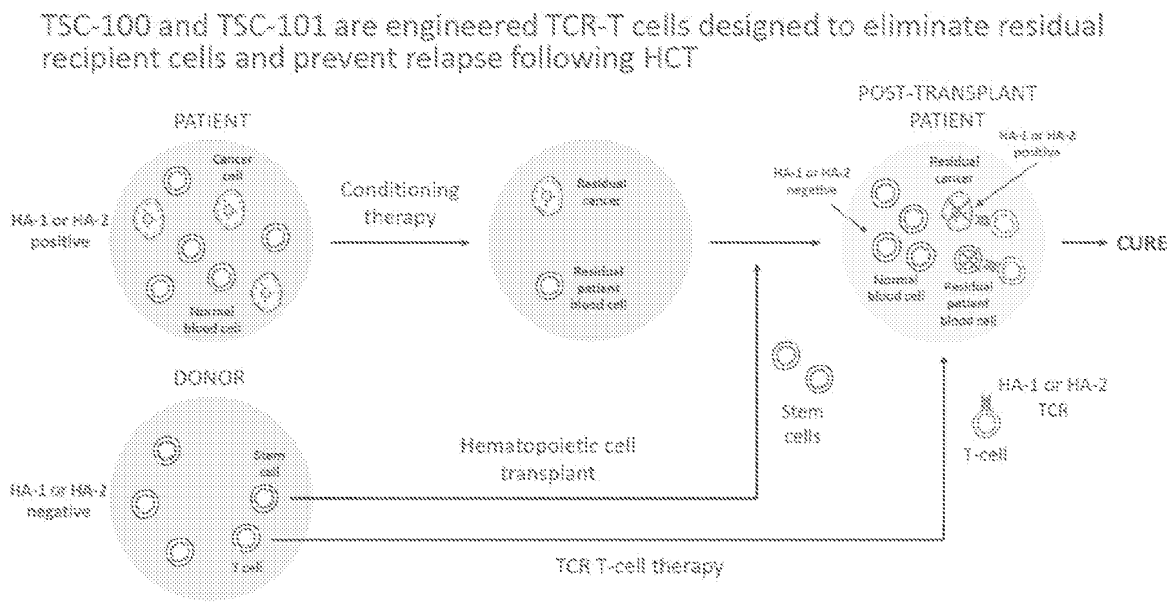

TSC-100 and TSC-101 are engineered TCR-T cells designed to eliminate residual recipient cells and prevent relapse following HCT
PATIENT
Cancer cell
HA-1 or HA-2 positive
Normal blood cell
Conditioning therapy
Residual cancer
Residual patient blood cell
POST-TRANSPLANT PATIENT
HA-1 or HA-2 negative
HA-1 or HA-2 positive
Residual cancer
Normal blood cell
Residual patient blood cell
CURE
DONOR
HA-1 or HA-2 negative
Stem cell
T cell
Hematopoietic cell transplant
Stem cells
HA-1 or HA-2 TCR
T-cell
TCR T-cell therapy

FIG. 4

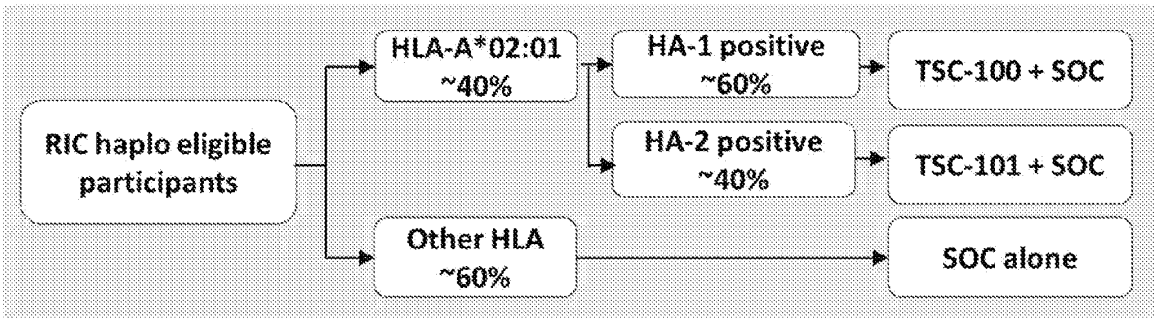

RIC haplo eligible participants
HLA-A*02:01 ~40%
Other HLA ~60%
HA-1 positive ~60%
HA-2 positive ~40%
TSC-100 + SOC
TSC-101 + SOC
SOC alone

FIG. 5

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)

FIG. 6

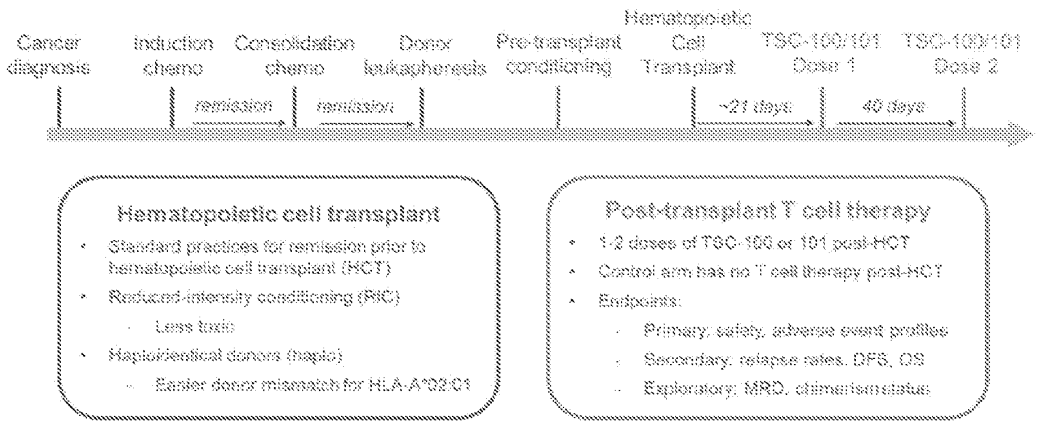

Cancer diagnosis
Induction chemo
Consolidation chemo
Donor leukapheresis
Pre-transplant conditioning
Hematopoietic Cell Transplant
TSC-100/101 Dose 1
TSC-100/101 Dose 2
remission
remission
~21 days
40 days
Hematopoietic cell transplant
Standard practices for remission prior to hematopoietic cell transplant (HCT)
Reduced-intensity conditioning (RIC)
Less toxic
Haploidentical donors (haplo)
Easier donor mismatch for HLA-A*02:01
Post-transplant T cell therapy
1-2 doses of TSC-100 or 101 post-HCT
Control arm has no T cell therapy post-HCT
Endpoints:
Primary: safety, adverse event profiles
Secondary: relapse rates, DFS, OS
Exploratory: MRD, chimerism status

FIG. 7

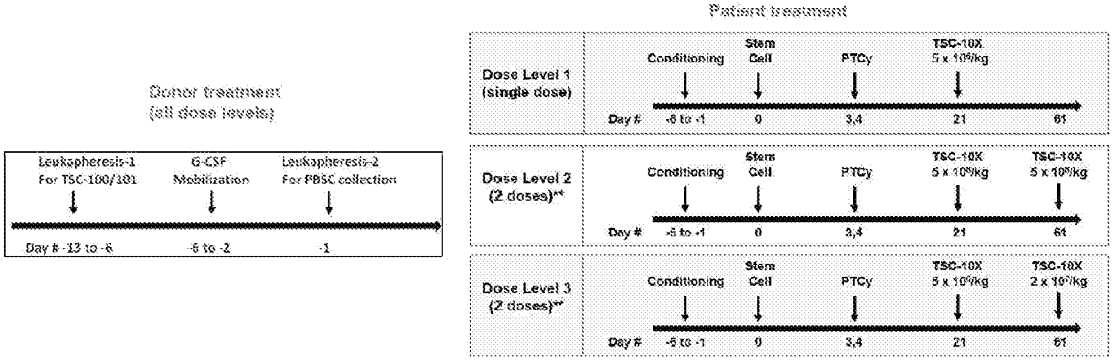

Donor treatment
(all dose levels)
Leukapheresis-1
For TSC-100/101
G-CSF
Mobilization
Leukapheresis-2
For PBSC collection
Day # -13 to -6
-5 to -2
-1
Patient treatment
Dose Level 1
(single dose)
Conditioning
Stem
Cell
PTCy
TSC-10X
5 x 10⁶/kg
Day #
-6 to -1
0
3,4
21
61
Dose Level 2
(2 doses)**
TSC-10X
5 x 10⁶/kg
Dose Level 3
(2 doses)**
TSC-10X
2 x 10⁷/kg

FIG. 8

	TSC-100				TSC-101				Control Arm			
Patient ID	P-0016-0014	P-0017-0001	P-0004-0007	P-0006-0003	P-0014-0001	P-0018-0005	P-0004-0008	P-0018-0008	P-0002-0001	P-0017-0001	P-0006-0001	P-0006-0002
Diagnosis	T-ALL	AML	AML	MDS	MDS	AML	B-ALL	B-ALL	MDS	MDS	MDS	AML
Molecular Markers	KMT2A-r/PTD	FLT3-ITD	Trisomy 8 IDH2 NRAS ASXL1	SRSF2 ASXL1 STAG2	DNMT3A mTP53	IDH1, SRSF2 ASXL1 CUX1	n/a	n/a	Trisomy 8, SRSF2 ASXL1	None	DNMT3A Monos 7 mTP53	Monos 7, RUNX1, EZH2
Pre-HCT MRD	Positive	Negative	Positive	Positive	Positive	Positive	Negative	Pending	Positive	Negative	Positive	Pending
RIC regimen	Flu/Cy/TBI	Flu/Bu4/Flu	Flu/Mel/TBI	Flu/Cy/TBI	Flu/Mel/TBI	Flu/Mel/TBI	Flu/Bu4/TBI	Flu/Bu4/TBI	Flu/Cy/TBI	Flu/Cy/TBI	Flu/Mel/TBI	Flu/Cy/TBI
HCT date	21 Mar 2023	27 Apr 2023	09 Sep 2022	31 Oct 2023	10 Feb 2023	20 Apr 2023	23 Jun 2022	06 Oct 2023	01 Nov 2023	01 Feb 2023	19 May 2023	23 Aug 2022
Dose Level	DL1	DL2	DL3	DL3	DL1	sDL2*	DL2	sDL3*	N/A			
PCR-T treatment day	#1 Day 39	#1 Day 35 #2 Day 76	#1 Day 34 #2 Day 75	#1 Day 37 #2 Day 84 †	#1 Day 31	#1 Day 77 #2 Day 82	#1 Day 33 #2 Day 62	#1 Day 37 #2 Day 70*	N/A			

§ Dose did not meet target dose criteria, * administered dosing

FIG. 9

A

Arm Dose Level	Patient ID	Grade*	Adverse Event	Treatment Day of Onset	Duration	TSC relatedness
TSC-100-DL2	P-003-0002	Grade 1	CRS	+0	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	+2	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-003-0004	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

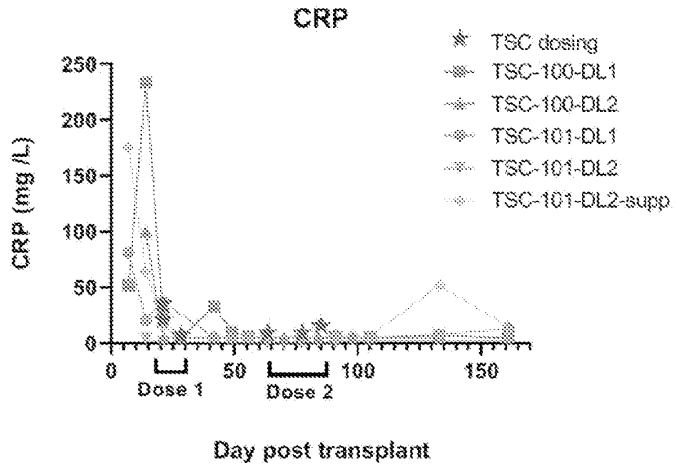


FIG. 10

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-DL2 exp	P-003-0005	Pyrexia	3	+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	3	+148	Not Related
TSC-101-DL1	P-004-0001	Interstitial pneumonitis	2	+167	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

FIG. 11

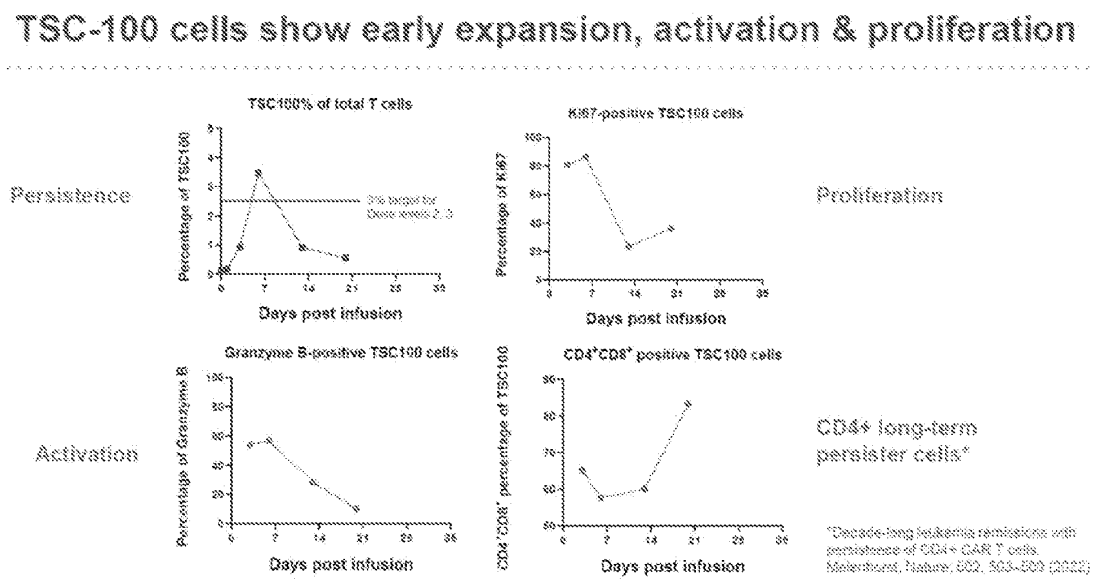

TSC-100 cells show early expansion, activation & proliferation
Persistence
TSC100% of total T cells
Percentage of TSC100
Days post infusion
Ki67-positive TSC100 cells
Percentage of Ki67
Days post infusion
Proliferation
Activation
Granzyme B-positive TSC100 cells
Percentage of Granzyme B
Days post infusion
CD4+CD8+ positive TSC100 cells
CD4+ CD8+ percentage of TSC100
Days post infusion
CD4+ long-term persister cells*
*Decade-long leukemia remissions with persistence of CD4+ CAR T cells. Melenhorst, Nature, 602, 503-509 (2022)

FIG. 12

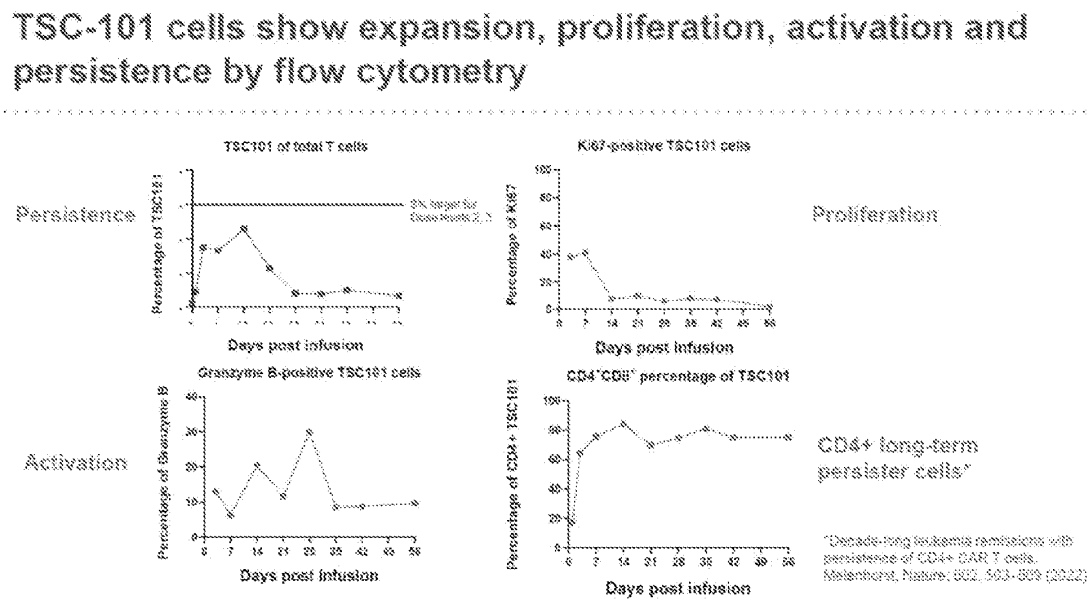

TSC-101 cells show expansion, proliferation, activation and persistence by flow cytometry
Persistence
TSC101 of total T cells
Days post infusion
Proliferation
Ki67-positive TSC101 cells
Days post infusion
Activation
Granzyme B-positive TSC101 cells
Days post infusion
CD4+long-term persister cells*
CD4+CD8+ percentage of TSC101
Days post infusion
*Decade-long leukemia remissions with persistence of CD4+ CAR T cells. Melenhorst, Nature, 602, 503-509 (2022)

FIG. 13

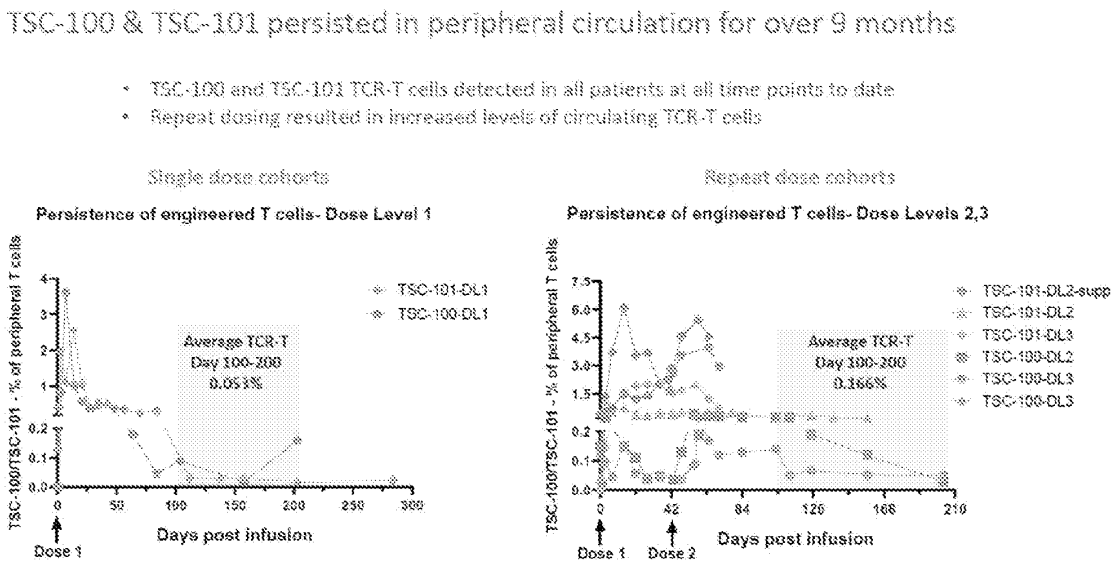

TSC-100 & TSC-101 persisted in peripheral circulation for over 9 months
• TSC-100 and TSC-101 TCR-T cells detected in all patients at all time points to date
• Repeat dosing resulted in increased levels of circulating TCR-T cells
Single dose cohorts
Repeat dose cohorts
Persistence of engineered T cells- Dose Level 1
TSC-100/TSC-101 - % of peripheral T cells
TSC-101-DL1
TSC-100-DL1
Average TCR-T
Day 100-200
0.051%
Days post infusion
Dose 1
Persistence of engineered T cells- Dose Levels 2,3
TSC-101-DL2-supp
TSC-101-DL2
TSC-101-DL3
TSC-100-DL2
TSC-100-DL3
Average TCR-T
Day 100-200
0.166%
Dose 1
Dose 2

FIG. 14

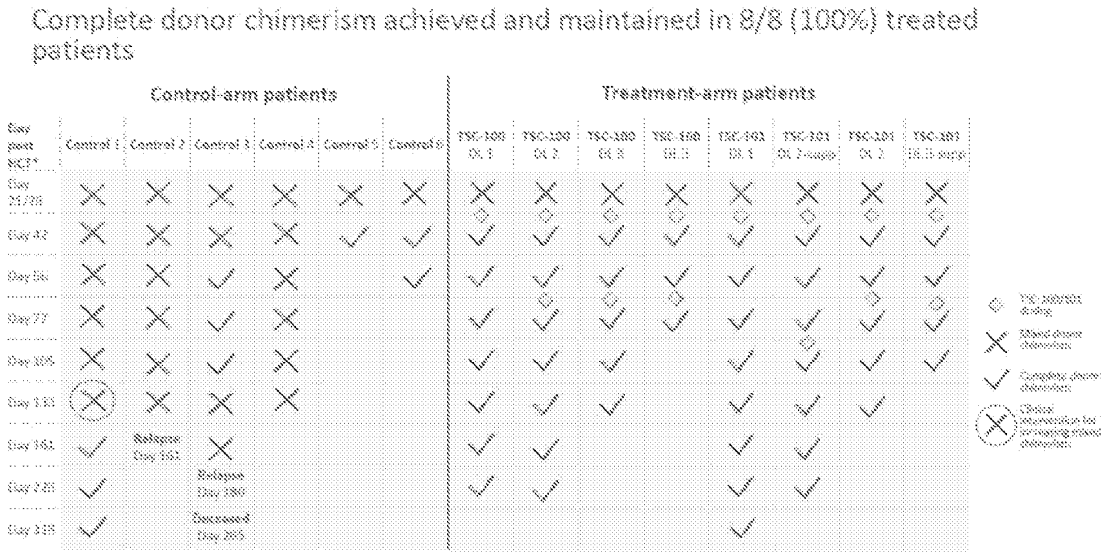

Complete donor chimerism achieved and maintained in 8/8 (100%) treated patients
Control-arm patients
Treatment-arm patients
Control 1
Control 2
Control 3
Control 4
Control 5
Control 6
Relapse Day 161
Relapse Day 180
Deceased Day 205

FIG. 15

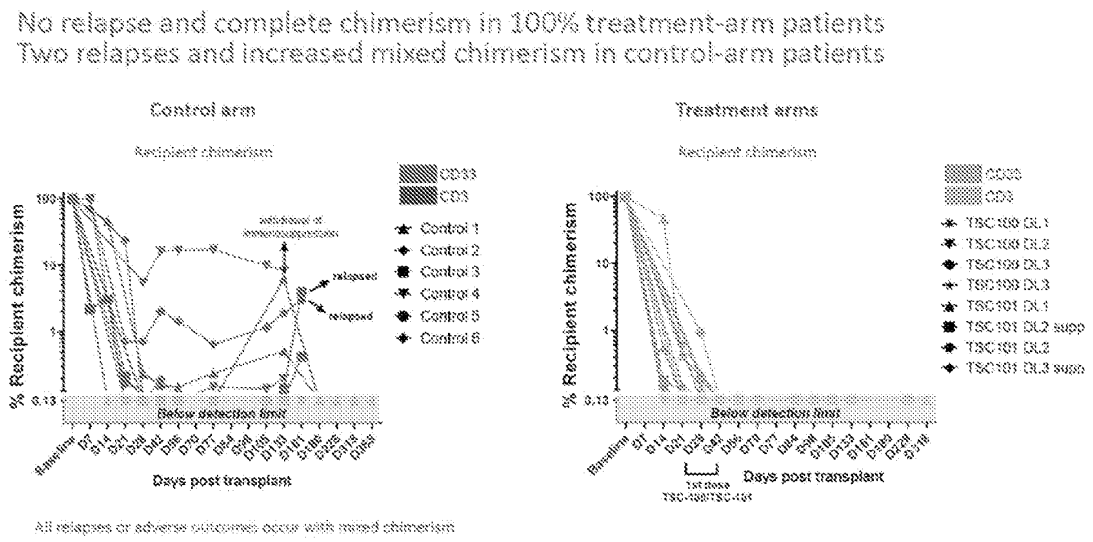

No relapse and complete chimerism in 100% treatment-arm patients
Two relapses and increased mixed chimerism in control-arm patients
Control arm
Recipient chimerism
CD33
CD3
% Recipient chimerism
100
10
1
0.13
Below detection limit
Control 1
Control 2
Control 3
Control 4
Control 5
Control 6
relapsed
relapsed
Baseline
D7
D14
D21
D28
D42
D56
D70
D77
D84
D105
D119
D161
D196
D224
D252
Days post transplant
Treatment arms
Recipient chimerism
CD33
CD3
% Recipient chimerism
100
10
1
0.13
Below detection limit
TSC100 DL1
TSC100 DL2
TSC100 DL3
TSC100 DL3
TSC101 DL1
TSC101 DL2 supp
TSC101 DL2
TSC101 DL3 supp
Baseline
D7
D14
D21
D28
D42
D56
D70
D77
D84
D105
D133
D161
D189
D224
D318
1st dose
Days post transplant
All relapses or adverse outcomes occur with mixed chimerism

FIG. 16

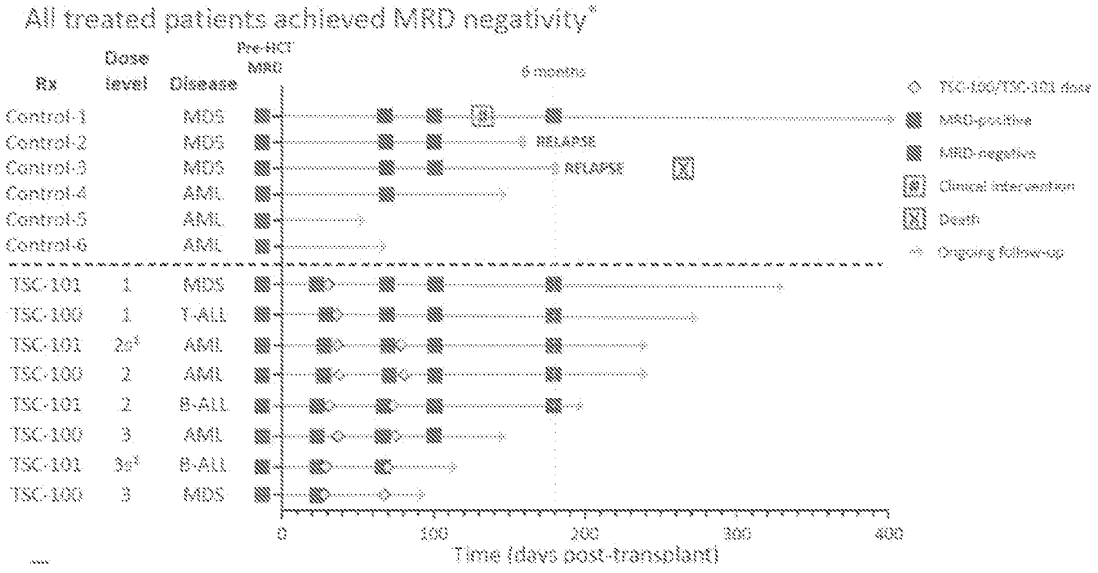

All treated patients achieved MRD negativity*
Rx
Dose level
Disease
Pre-HCT MRD
6 months
Control-1 MDS
Control-2 MDS
Control-3 MDS
Control-4 AML
Control-5 AML
Control-6 AML
TSC-101 1 MDS
TSC-100 1 T-ALL
TSC-101 2a[3] AML
TSC-100 2 AML
TSC-101 2 B-ALL
TSC-100 3 AML
TSC-101 3a[3] B-ALL
TSC-100 3 MDS
RELAPSE
RELAPSE
0
100
200
300
400
Time (days post-transplant)
TSC-100/TSC-101 dose
MRD-positive
MRD-negative
Clinical intervention
Death
Ongoing follow-up

FIG. 17

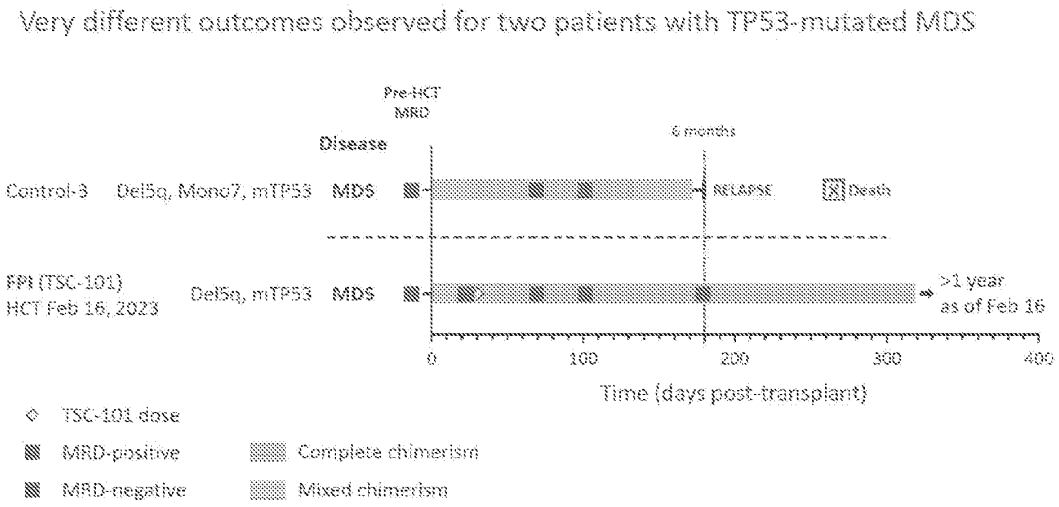
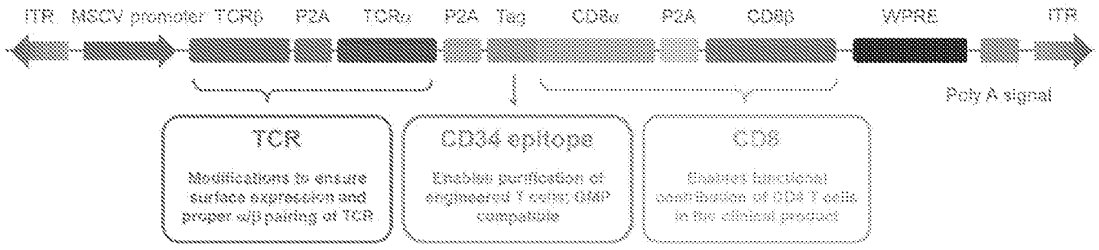

Very different outcomes observed for two patients with TP53-mutated MDS
Pre-HCT MRD
Disease
6 months
Control-3
Del5q, Monc7, mTP53
MDS
RELAPSE
Death
FPI (TSC-101)
HCT Feb 16, 2023
Del5q, mTP53
MDS
>1 year as of Feb 16
0
100
200
300
400
Time (days post-transplant)
TSC-101 dose
MRD-positive
MRD-negative
Complete chimerism
Mixed chimerism

FIG. 18



Key: CD: Cluster of Differentiation, ITR: Inverted Terminal Repeat, npDNA: Nanoplasmid DNA, MSCV: Murine Stem Cell Virus, TCR: T Cell Receptor, WPRE: Woodchuck Hepatitis Virus Post-Transcriptional Regulatory Element

FIG. 19

Map of the TSC-100 npDNA Transposon Vector Cassette

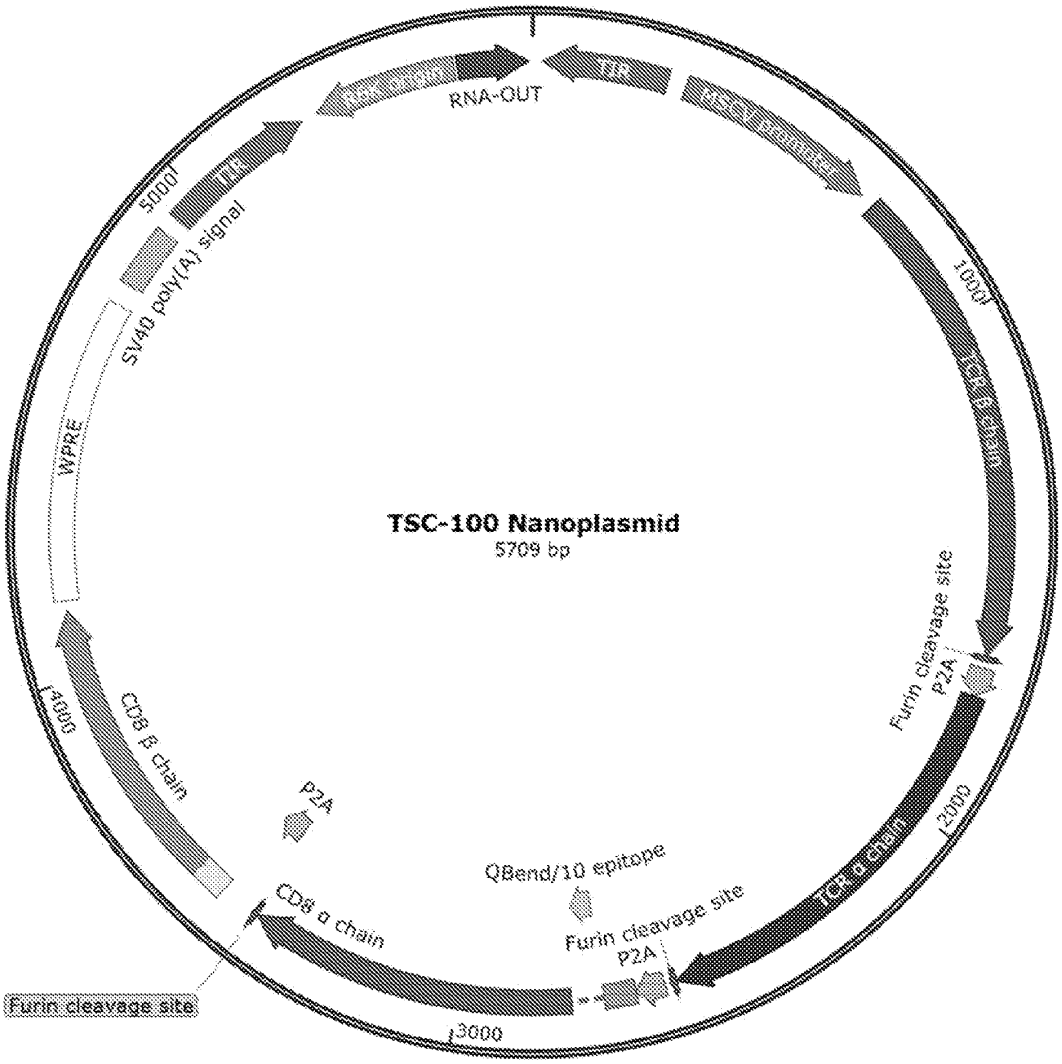
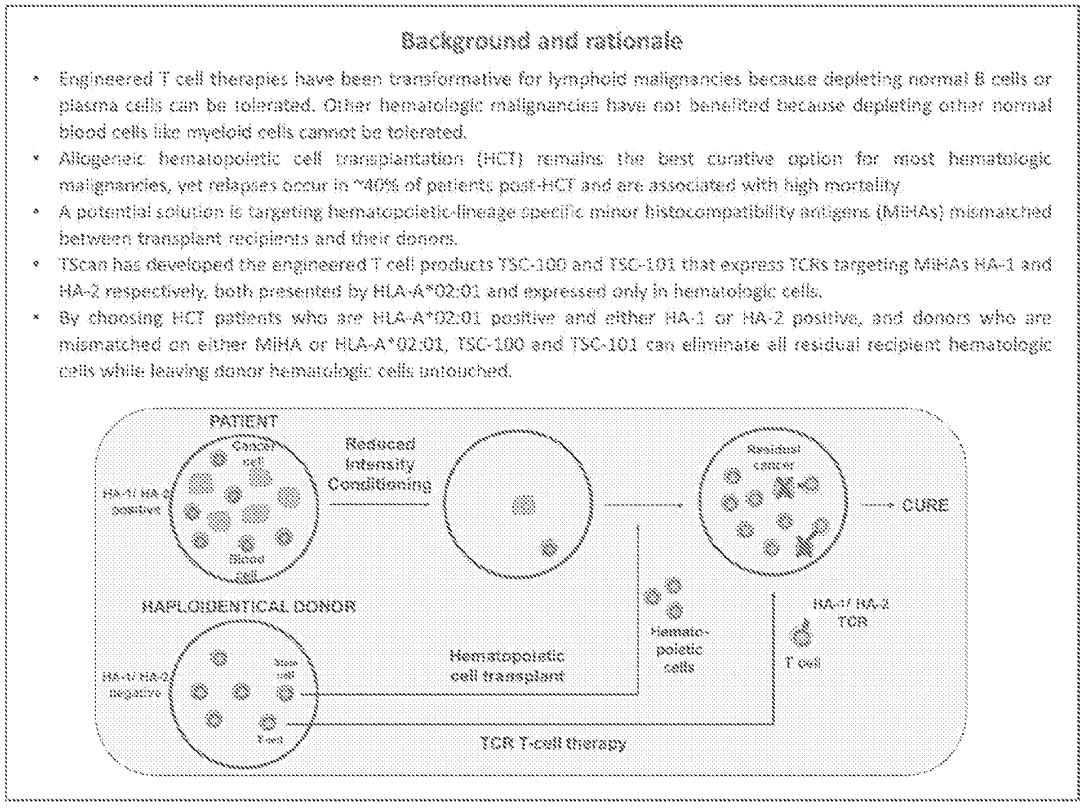


FIG. 20

Map of the TSC-101 npDNA Transposon Vector Cassette



FIG. 21


Background and rationale
Engineered T cell therapies have been transformative for lymphoid malignancies because depleting normal B cells or plasma cells can be tolerated. Other hematologic malignancies have not benefited because depleting other normal blood cells like myeloid cells cannot be tolerated.
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 (MiHAs) 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 can eliminate all residual recipient hematologic cells while leaving donor hematologic cells untouched.
PATIENT
Cancer cell
HA-1/ HA-2 positive
Blood cell
Reduced Intensity Conditioning
Residual cancer
CURE
HAPLOIDENTICAL DONOR
HA-1/ HA-2 negative
Stem cell
T cell
Hematopoietic cell transplant
Hematopoietic cells
HA-1/ HA-2 TCR
T cell
TCR T-cell therapy

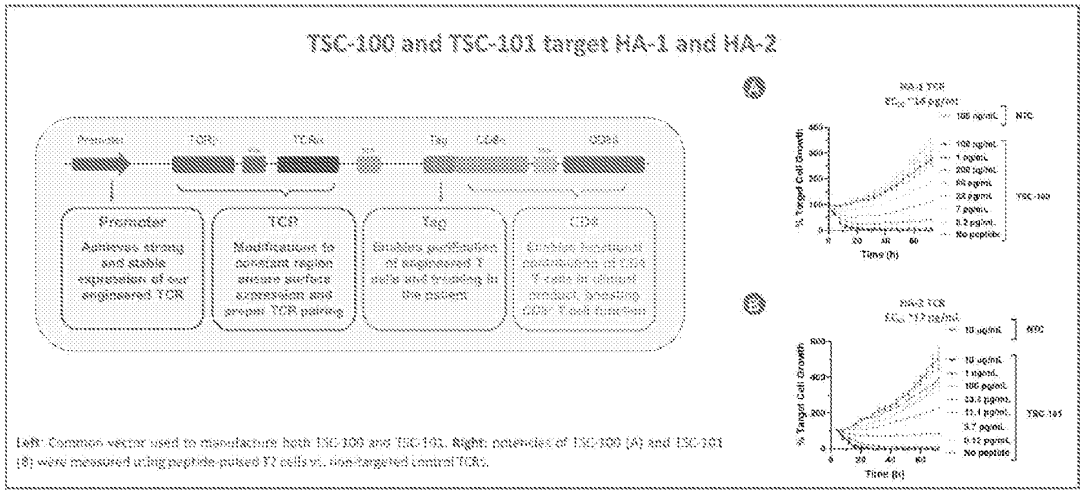
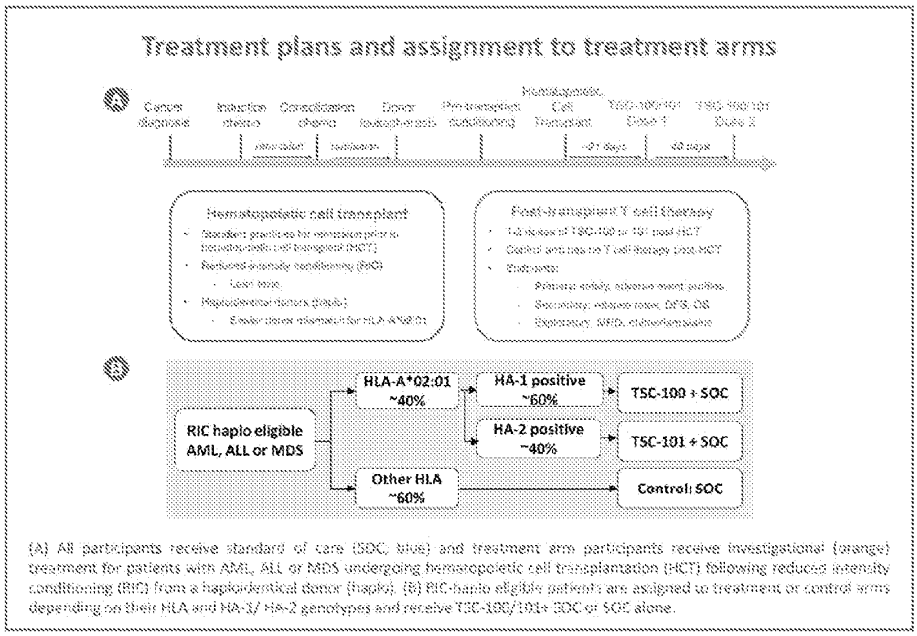
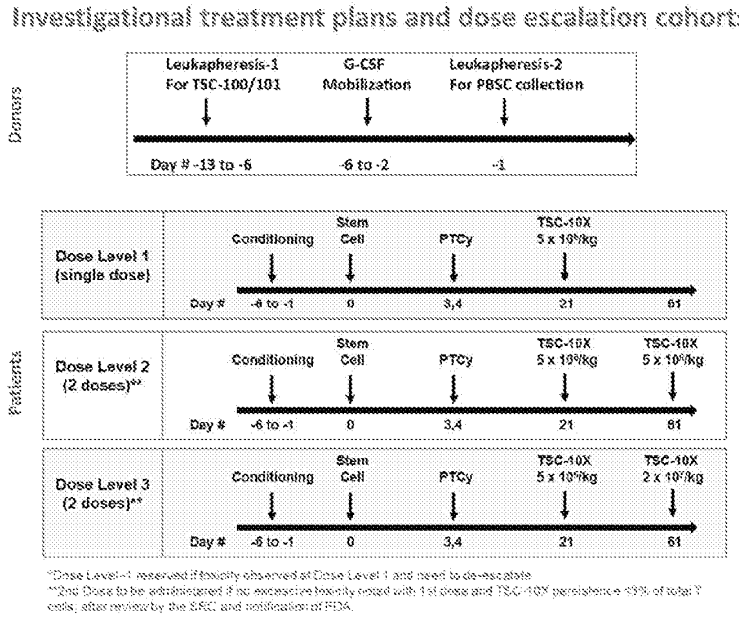

TSC-100 and TSC-101 target HA-1 and HA-2
Promoter
TCRβ
TCRα
Tag
CD8α
CD8β
Promoter
Achieves strong and stable expression of our engineered TCR
TCR
Modifications to constant region ensure surface expression and proper TCR pairing
Tag
Enables purification of engineered T cells and tracking in the patient
CD8
Enables functional reconstitution of CD8 T cells in clinical product, boosting CD8+ T cell function
HA-1 TCR
NTC
100 ng/mL
1 ng/mL
200 pg/mL
66 pg/mL
22 pg/mL
7 pg/mL
2.2 pg/mL
No peptide
TSC-100
% Target Cell Growth
Time (h)
HA-2 TCR
10 ug/mL
1 ug/mL
100 pg/mL
33.3 pg/mL
11.1 pg/mL
3.7 pg/mL
1.12 pg/mL
No peptide
TSC-101
Left: Common vector used to manufacture both TSC-100 and TSC-101. Right: potencies of TSC-100 (A) and TSC-101 (B) were measured using peptide-pulsed T2 cells vs. non-targeted control TCRs.

FIG. 22



(A) All participants receive standard of care (SOC, blue) and treatment arm participants receive investigational (orange) treatment for patients with AML, ALL or MDS undergoing hematopoietic cell transplantation (HCT) following reduced intensity conditioning (RIC) from a haploidentical donor (haplo). (B) RIC-haplo eligible patients are assigned to treatment or control arms depending on their HLA and HA-1/ HA-2 genotypes and receive TSC-100/101+ SOC or SOC alone.



*Dose Level -1 reserved if toxicity observed at Dose Level 1 and need to de-escalate
**2nd Dose to be administered if no excessive toxicity noted with 1st dose and TSC-10X persistence <5% of total T cells, after review by the SRC and notification of FDA

Investigational treatment plans for donors (top) or patients (bottom). Donors undergo two rounds of leukapheresis, first before G-CSF mobilization, to manufacture TSC-100/101, and second after mobilization, for standard peripheral blood stem cell collection. Patients receive conditioning therapy from Days -6 to -1, stem cell infusions on Day 0, post-transplant cyclophosphamide (PTCy) on Days 3,4 then upon count recovery (around Day 21), receive the 1st dose of TSC-100 or 101. In Dose Levels 2 and 3, a second dose is administered at least 40 days after the 1st dose. In Dose Level 3, the 2nd dose is escalated by 4-fold. Dose escalation rules follow the interval 3+3 design1 with 3-12 patients per cohort. The study is currently enrolling patients at Dose Level 3.

FIG. 23

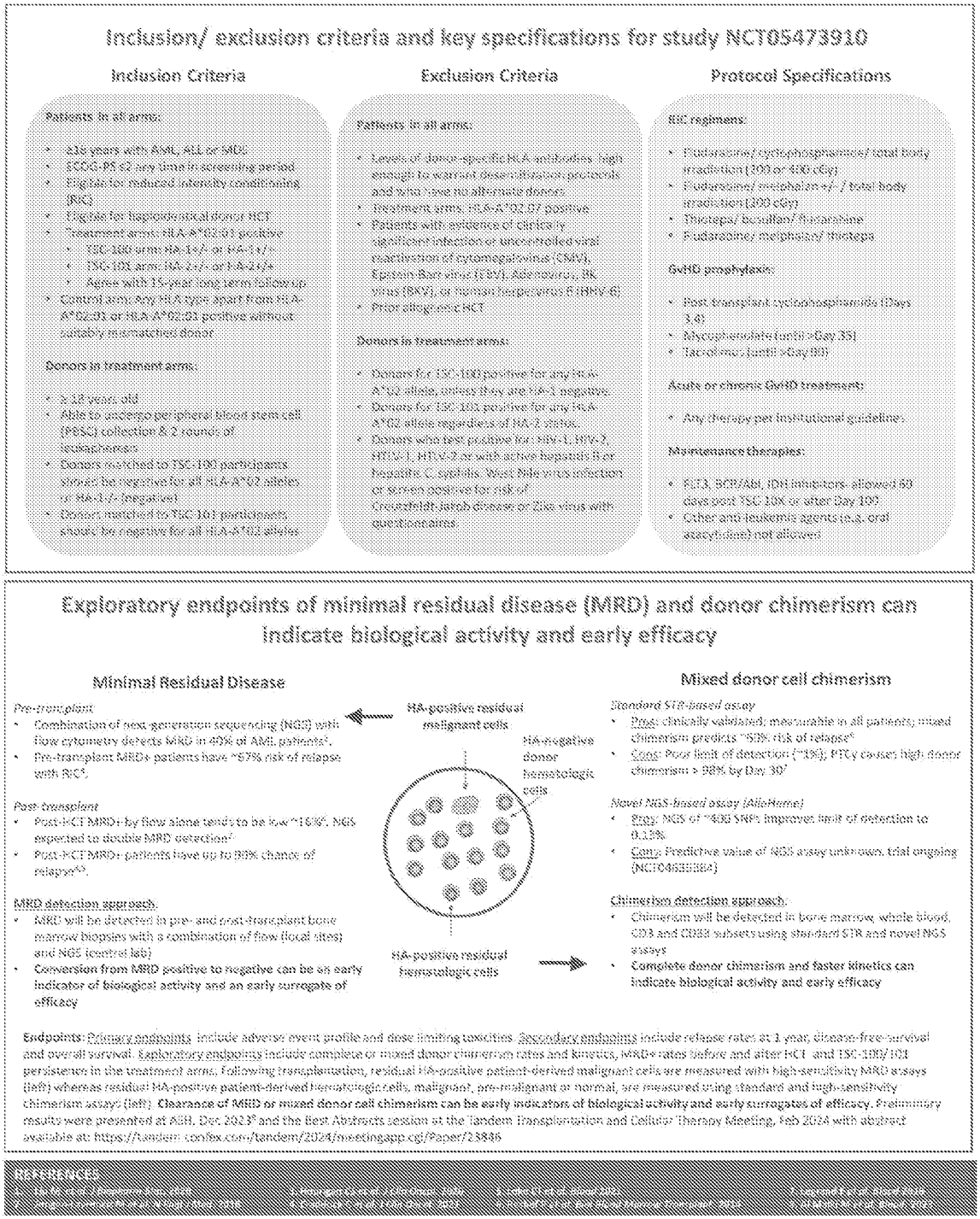

Inclusion/ exclusion criteria and key specifications for study NCT05473910
Inclusion Criteria
Patients in all arms:
≥16 years with AML, ALL or MDS
ECOG PS ≤2 any time in screening period
Eligible for reduced intensity conditioning (RIC)
Eligible for haploidentical donor HCT
Treatment arms: HLA-A*02:01 positive
TSC-100 arm: HA-1+/- or HA-1+/+
TSC-101 arm: HA-1+/- or HA-1+/+
Agree with 15-year long term follow up
Control arm: Any HLA type apart from HLA-A*02:01 or HLA-A*02:01 positive without suitably mismatched donor
Donors in treatment arms:
≥ 18 years old
Able to undergo peripheral blood stem cell (PBSC) collection & 2 rounds of leukapheresis
Donors matched to TSC-100 participants should be negative for all HLA-A*02 alleles or HA-1+/- (negative)
Donors matched to TSC-101 participants should be negative for all HLA-A*02 alleles
Exclusion Criteria
Patients in all arms:
Levels of donor-specific HLA antibodies high enough to warrant desensitization protocols and who have no alternate donors
Treatment arms: HLA-A*02:07 positive
Patients with evidence of clinically significant infection or uncontrolled viral reactivation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), Adenovirus, BK virus (BKV), or human herpesvirus 6 (HHV-6)
Prior allogeneic HCT
Donors in treatment arms:
Donors for TSC-100 positive for any HLA-A*02 allele, unless they are HA-1 negative.
Donors for TSC-101 positive for any HLA-A*02 allele regardless of HA-1 status.
Donors who test positive for: Hiv-1, HIV-2, HTLV-1, HTLV-2 or with active hepatitis B or hepatitis C, syphilis, West Nile virus infection or screen positive for risk of Creutzfeldt-Jakob disease or Zika virus with questionnaire.
Protocol Specifications
RIC regimens:
Fludarabine/ cyclophosphamide/ total body irradiation (200 or 400 cGy)
Fludarabine/ melphalan +/- / total body irradiation (200 cGy)
Thiotepa/ busulfan/ fludarabine
Fludarabine/ melphalan/ thiotepa
GvHD prophylaxis:
Post-transplant cyclophosphamide (Days 3,4)
Mycophenolate (until >Day 35)
Tacrolimus (until >Day 80)
Acute or chronic GvHD treatment:
Any therapy per institutional guideline.
Maintenance therapies:
FLT3, BCR/Abl, IDH inhibitors, allowed 60 days post TSC 100 or after Day 100
Other anti-leukemia agents (e.g. oral azacytidine) not allowed
Exploratory endpoints of minimal residual disease (MRD) and donor chimerism can indicate biological activity and early efficacy
Minimal Residual Disease
Pre-transplant
Combination of next-generation sequencing (NGS) with flow cytometry detects MRD in 40% of AML patients[1].
Pre-transplant MRD+ patients have ~67% risk of relapse with RIC[2].
Post-transplant
Post-HCT MRD+ by flow alone tends to be low ~16%[3]. NGS expected to double MRD detection[3]
Post-HCT MRD+ patients have up to 80% chance of relapse[4,5].
MRD detection approach:
MRD will be detected in pre- and post-transplant bone marrow biopsies with a combination of flow (local sites) and NGS (central lab)
Conversion from MRD positive to negative can be an early indicator of biological activity and an early surrogate of efficacy
HA-positive residual malignant cells
HA-negative donor hematologic cells
HA-positive residual hematologic cells
Mixed donor cell chimerism
Standard STR-based assay
Pros: clinically validated; measurable in all patients; mixed chimerism predicts ~50% risk of relapse[6]
Cons: Poor limit of detection (~3%); PTCy causes high donor chimerism > 98% by Day 30[7]
Novel NGS-based assay (AlloHome)
Pros: NGS of ~400 SNPs improves limit of detection to 0.13%
Cons: Predictive value of NGS assay unknown, trial ongoing (NCT04633304)
Chimerism detection approach:
Chimerism will be detected in bone marrow, whole blood, CD3 and CD33 subsets using standard STR and novel NGS assays
Complete donor chimerism and faster kinetics can indicate biological activity and early efficacy
Endpoints: Primary endpoints include adverse event profile and dose limiting toxicities. Secondary endpoints include relapse rates at 1 year, disease-free-survival and overall survival. Exploratory endpoints include complete or mixed donor chimerism rates and kinetics, MRD+ rates before and after HCT and TSC-100/ IO1 persistence in the treatment arms. Following transplantation, residual HA-positive patient-derived malignant cells are measured with high-sensitivity MRD assays (left) whereas residual HA-positive patient-derived hematologic cells, malignant, pre-malignant or normal, are measured using standard and high-sensitivity chimerism assays (left). Clearance of MRD or mixed donor cell chimerism can be early indicators of biological activity and early surrogates of efficacy. Preliminary results were presented at ASH, Dec 2023[8] and the Best Abstracts session at the Tandem Transplantation and Cellular Therapy Meeting, Feb 2024 with abstract available at: https://tandem.confex.com/tandem/2024/meetingapp.cgi/Paper/23886
REFERENCES

FIG. 24

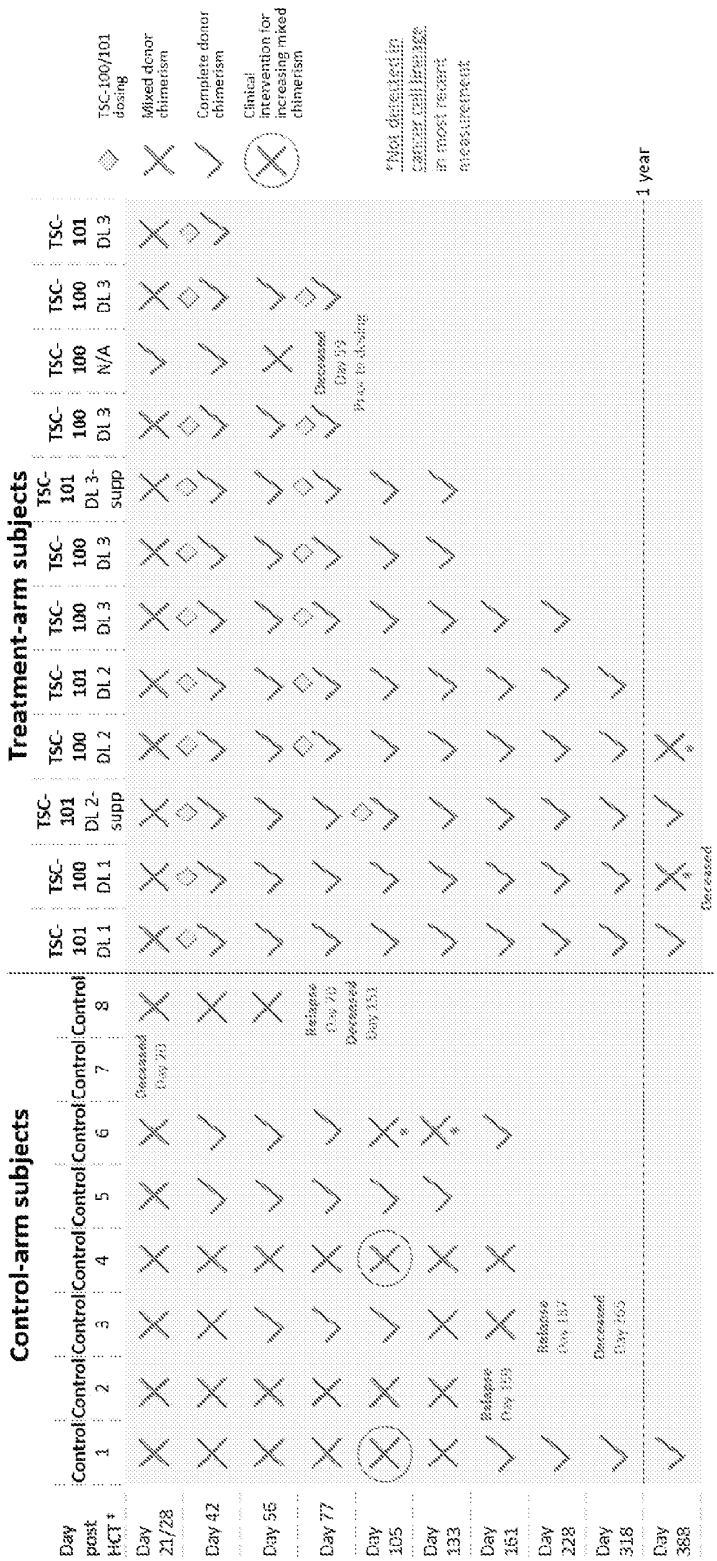

Control-arm subjects
Treatment-arm subjects
Day post HCT ¹
Control 1
Control 2
Control 3
Control 4
Control 5
Control 6
Control 7
Control 8
TSC-101 DL 1
TSC-100 DL 1
TSC-101 DL 2-supp
TSC-100 DL 2
TSC-101 DL 2
TSC-100 DL 3
TSC-101 DL 3-supp
TSC-100 DL 3
TSC-100 N/A
TSC-100 DL 3
TSC-101 DL 3
Relapse Day 168
Relapse Day 157
Deceased Day 165
Deceased Day 203
Relapse Day 70
Deceased Day 153
Prior to dosing
Deceased Day 153
Day 45: Unrelated second infection
Deceased
1 year
TSC-100/101 dosing
Mixed donor chimerism
Complete donor chimerism
Clinical intervention for increasing mixed chimerism
*Not detected in cancer cell lineage in most recent assessment
Day 21/28
Day 42
Day 56
Day 77
Day 105
Day 133
Day 161
Day 228
Day 318
Day 388

FIG. 25

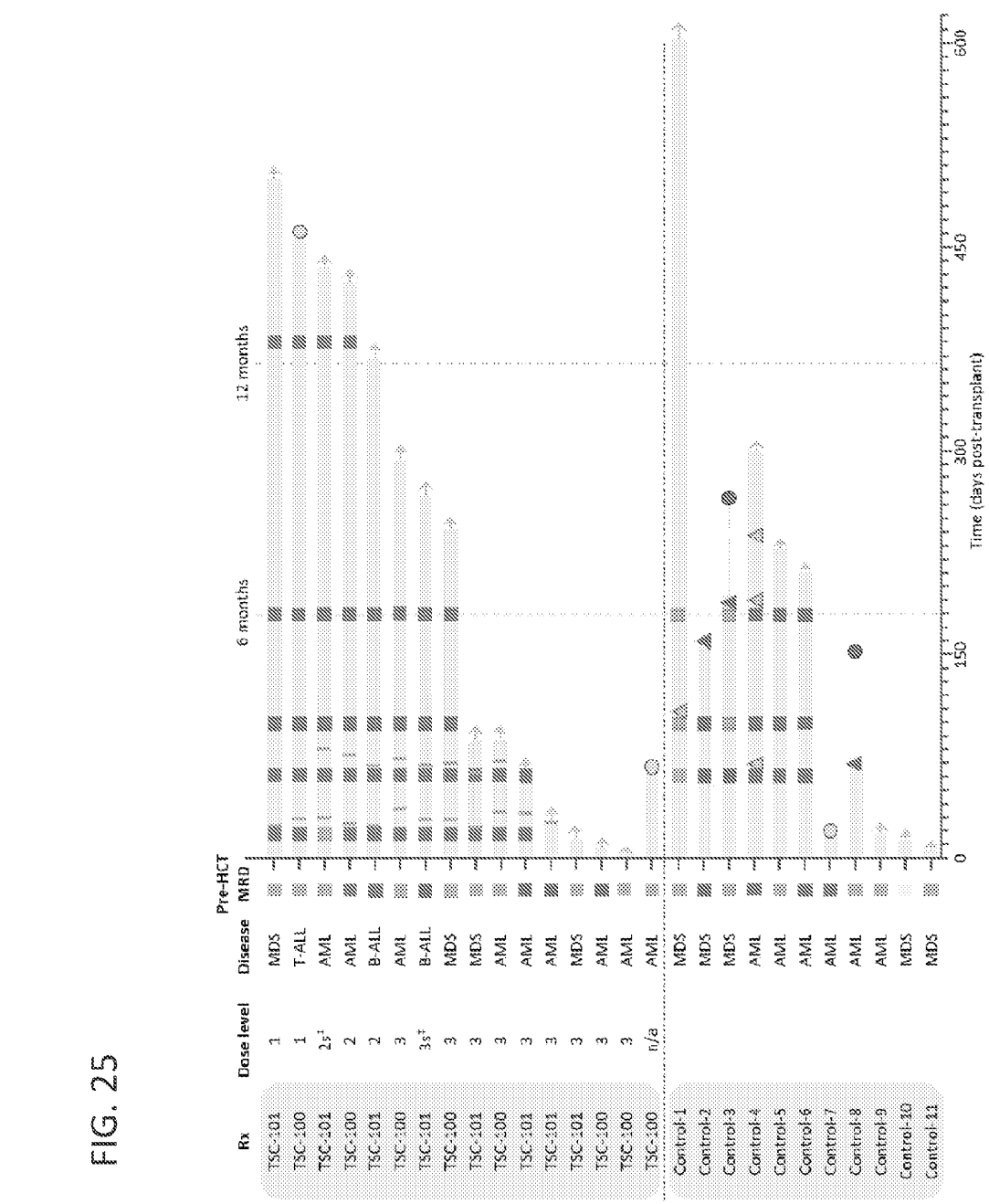

Rx
Dose level
Disease
Pre-HCT MRD
6 months
12 months
TSC-101
TSC-100
TSC-101
TSC-100
TSC-101
TSC-100
TSC-101
TSC-100
TSC-101
TSC-100
TSC-101
TSC-100
TSC-101
TSC-100
TSC-100
Control-1
Control-2
Control-3
Control-4
Control-5
Control-6
Control-7
Control-8
Control-9
Control-10
Control-11
1
1
2.5[1]
2
2
3
3.5[2]
3
3
3
3
3
3
3
3
n/a
MDS
T-ALL
AML
AML
B-ALL
AML
B-ALL
MDS
MDS
AML
AML
AML
MDS
AML
AML
AML
MDS
MDS
MDS
AML
AML
AML
AML
AML
AML
AML
AML
MDS
MDS
0
150
300
450
600
Time (days post-transplant)
TSC-100/TSC-101 infusion
Clinical intervention for concern for relapse
Relapse
Death from relapse
Death unrelated to relapse or TSC
Ongoing follow-up
MRD-positive
MRD-negative
MRD pending

FIG. 26

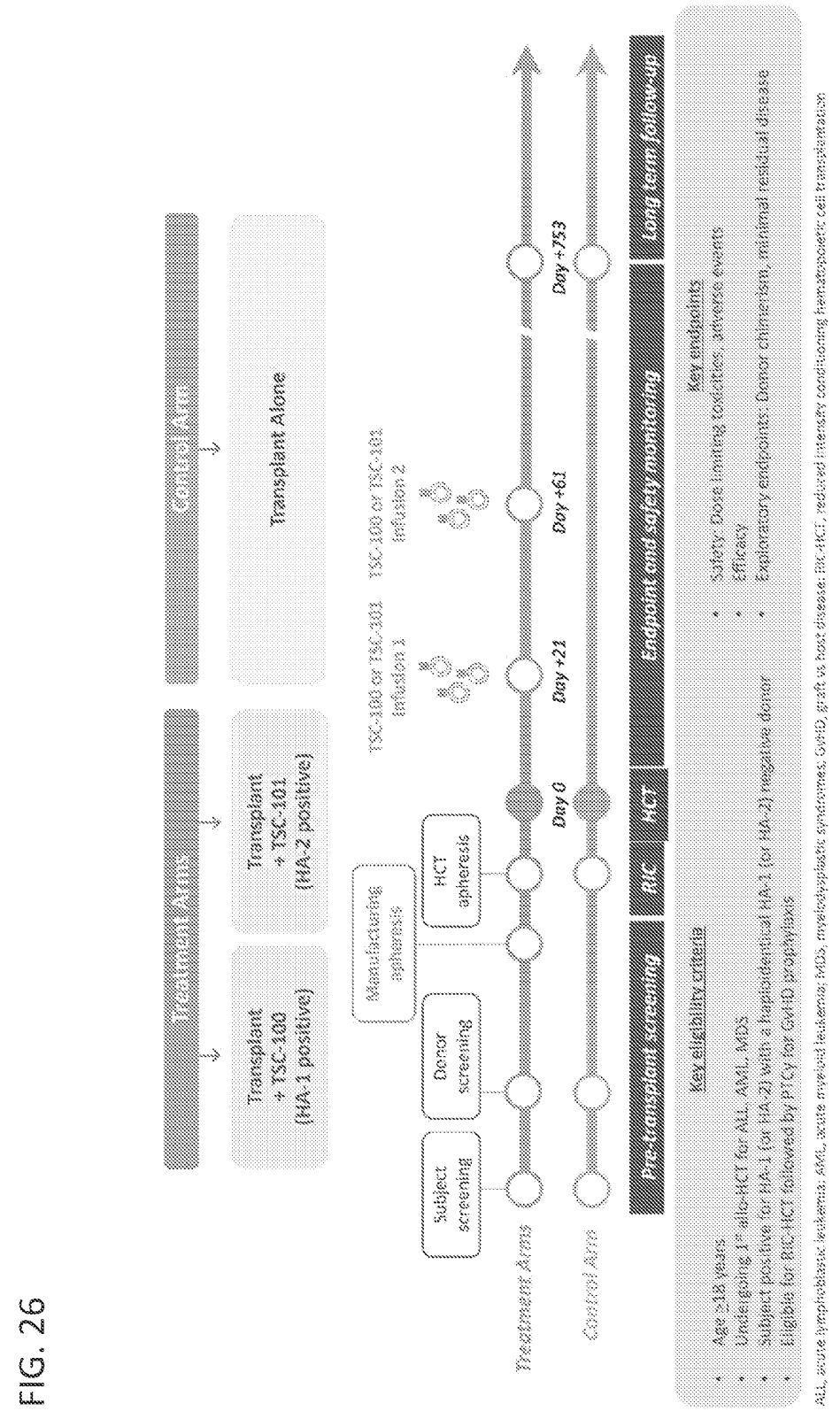

Treatment Arms
Control Arm
Transplant + TSC-300 (HA-1 positive)
Transplant + TSC-301 (HA-2 positive)
Transplant Alone
Subject screening
Donor screening
Manufacturing apheresis
HCT apheresis
TSC-300 or TSC-301 infusion 1
TSC-300 or TSC-301 infusion 2
Day 0
Day +21
Day +61
Day +753
Treatment
Pre-transplant screening
RIC
HCT
Endpoint and safety monitoring
Long term follow-up
Key eligibility criteria
Age ≥18 years
Undergoing 1st allo-HCT for ALL, AML, MDS
Subject positive for HA-1 (or HA-2) with a haploidentical HA-1 (or HA-2) negative donor
Eligible for RIC HCT followed by PTCy for GvHD prophylaxis
Key endpoints
Safety: Dose limiting toxicities, adverse events
Efficacy
Exploratory endpoints: Donor chimerism, minimal residual disease
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; GvHD, graft vs host disease; RIC HCT, reduced intensity conditioning hematopoietic cell transplantation

FIG. 27

		TSC-100	TSC-101	Any TSC	Control
Subjects Enrolled and assigned		14	12	26	13
Subjects Transplanted (efficacy data cohort)		14	12	26	12
Subjects Infused (safety data cohort)		10	12	22	N/A*
Median Time of Follow Up, months		4.0 (0-19)	6.4 (1-21)	5.1 (0-21)	7.1 (1-25)
Age, Median (Range)		69 (39-76)	66 (52-74)	67 (39-76)	66 (23-74)
Sex, Male (n, %)		10 (71%)	7 (58%)	17 (65%)	6 (46%)
Underlying Disease	ALL	2	2	4	0
	AML	10	7	17	8
	MDS	2	3	5	5
Genetics/ cytogenetics	**TP53 mutated**	**4**	**2**	**6**	**2**
	FLT3 mutation	2	0	2	5
	Adverse Risk**	11	10	21	8
Pre-HCT MRD Positive		8	5	13	7
MRD positive or adverse risk genetics		11/14	10/12	21/26	10/13

FIG. 28

Dose Level	Planned Day of Infusion Post HCT		DSC100 N=10	DSC101 N=12
	+21	+61		
DL1	5×10^5 TCR-T cells/kg	N/A	1	1
DL2	5×10^6 TCR-T cells/kg	5×10^6 TCR-T cells/kg	1	2
DL3	5×10^6 TCR-T cells/kg	2×10^7 TCR-T cells/kg	8	9

FIG. 29

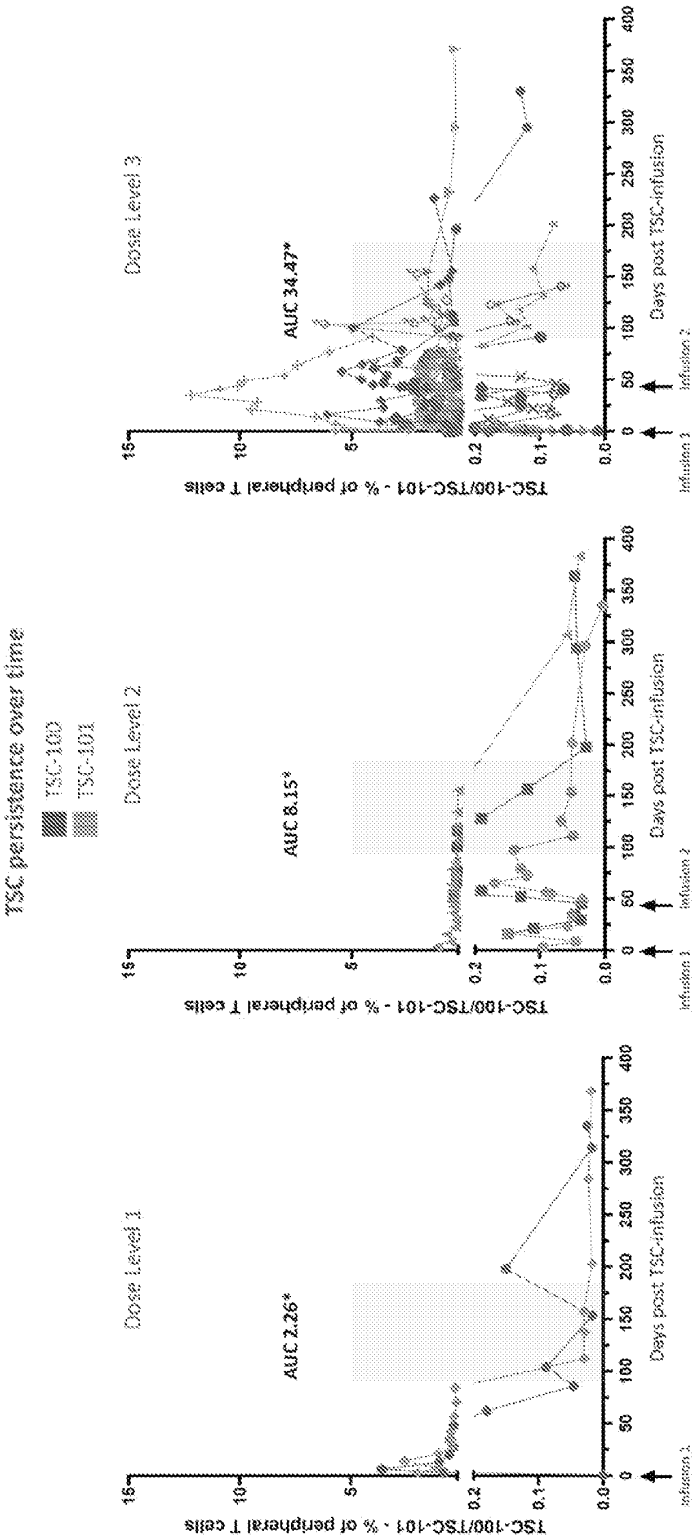

TSC persistence over time
TSC-100
TSC-101
Dose Level 1
Dose Level 2
Dose Level 3
AUC 2.26*
AUC 8.15*
AUC 34.47*
TSC-100/TSC-101 - % of peripheral T cells
Days post TSC-infusion
Infusion 1
Infusion 2

FIG. 30

CTCAE	TSC-100 n=10	TSC-101 n=13	Any TSC n=23	Control n=12
Any Acute GvHD	6 (60%)	7 (58%)	13 (62%)	5 (41%)
Grade 1	4 (40%)	3 (25%)	7 (32%)	2 (17%)
Grade 2 - 4	2 (20%)	4 (33%)	6 (27%)	3 (25%)
Any Chronic GvHD	1 (10%)	0 (0%)	1 (5%)	1 (8%)
Grade 1	1 (10%)	0 (0%)	1 (5%)	1 (8%)
Grade 2 - 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any CRS	4 (40%)	8 (67%)	12 (57%)	6 (50%)
Grade 1 - 2	4 (40%)	8 (67%)	12 (57%)	6 (50%)
Grade 3 - 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-emergent CRS	1 (10%)	1 (8%)	2 (9%)	NA
Grade 1 - 2	1 (10%)	1 (8%)	2 (9%)	NA
Grade 3 - 4	0 (0%)	0 (0%)	0 (0%)	NA
Any ICANS	0 (0%)	0 (0%)	0 (0%)	0 (0%)

FIG. 31

Events in >5% of subjects	Any TSC n=22	Control n=12
Anemia	7 (31.8)	2 (16.7)
Platelet count decreased	4 (18.2)	3 (25.0)
Neutrophil count decreased	3 (13.6)	1 (8.3)
Pneumonia	3 (13.6)	1 (8.3)
Sepsis	3 (13.6)	0
Decreased appetite	2 (9.1)	0
Rash maculo-papular	2 (9.1)	0
Acute graft vs host disease	1 (4.5)	1 (8.3)
Hypertension	1 (4.5)	1 (8.3)
Hypokalemia	1 (4.5)	1 (8.3)
Hypoxia	1 (4.5)	1 (8.3)
Pancytopenia	1 (4.5)	1 (8.3)
Neck pain	0	2 (16.7)
Acute graft vs host disease in skin	0	1 (8.3)
Graft vs host disease in skin	0	1 (8.3)
Graft vs host disease in GI tract	0	1 (8.3)
Alanine aminotransferase increased	0	1 (8.3)
Aspartate aminotransferase increased	0	1 (8.3)
Gamma-glutamyltransferase increased	0	1 (8.3)
Muscular weakness	0	1 (8.3)
Pneumonia respiratory syncytial viral	0	1 (8.3)

FIG. 32

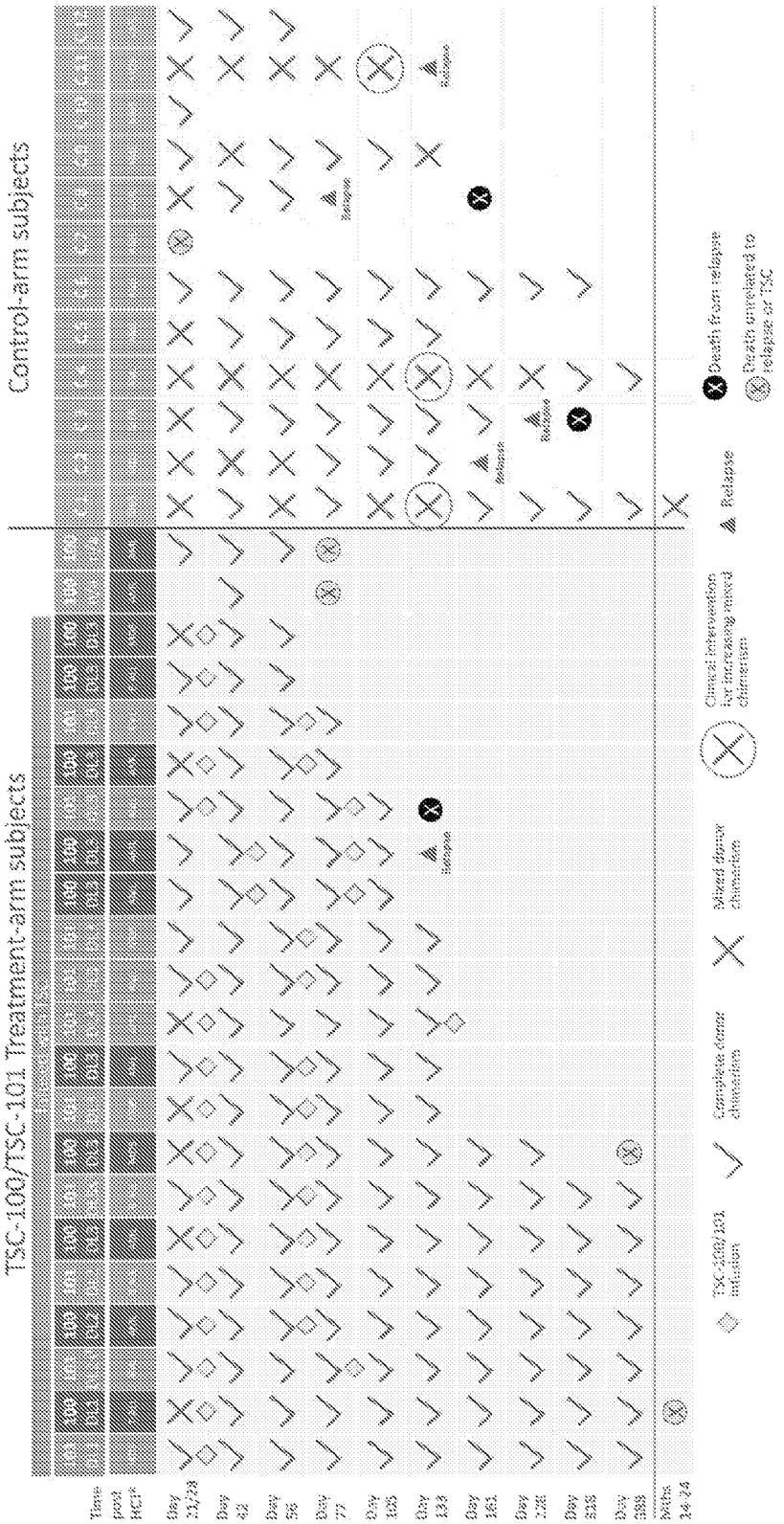

TSC-100/TSC-101 Treatment-arm subjects
Control-arm subjects
Time post HCT
Day -2/28
Day 42
Day 56
Day 77
Day 105
Day 133
Day 161
Day 196
Day 224
Day 252
Day 280
Months 14-24
TSC-100/101 initiation
Complete dose diminution
Mixed dose diminution
Clinical intervention for increasing mixed chimerism
Relapse
Death from relapse
Death unrelated to relapse or TSC

FIG. 33

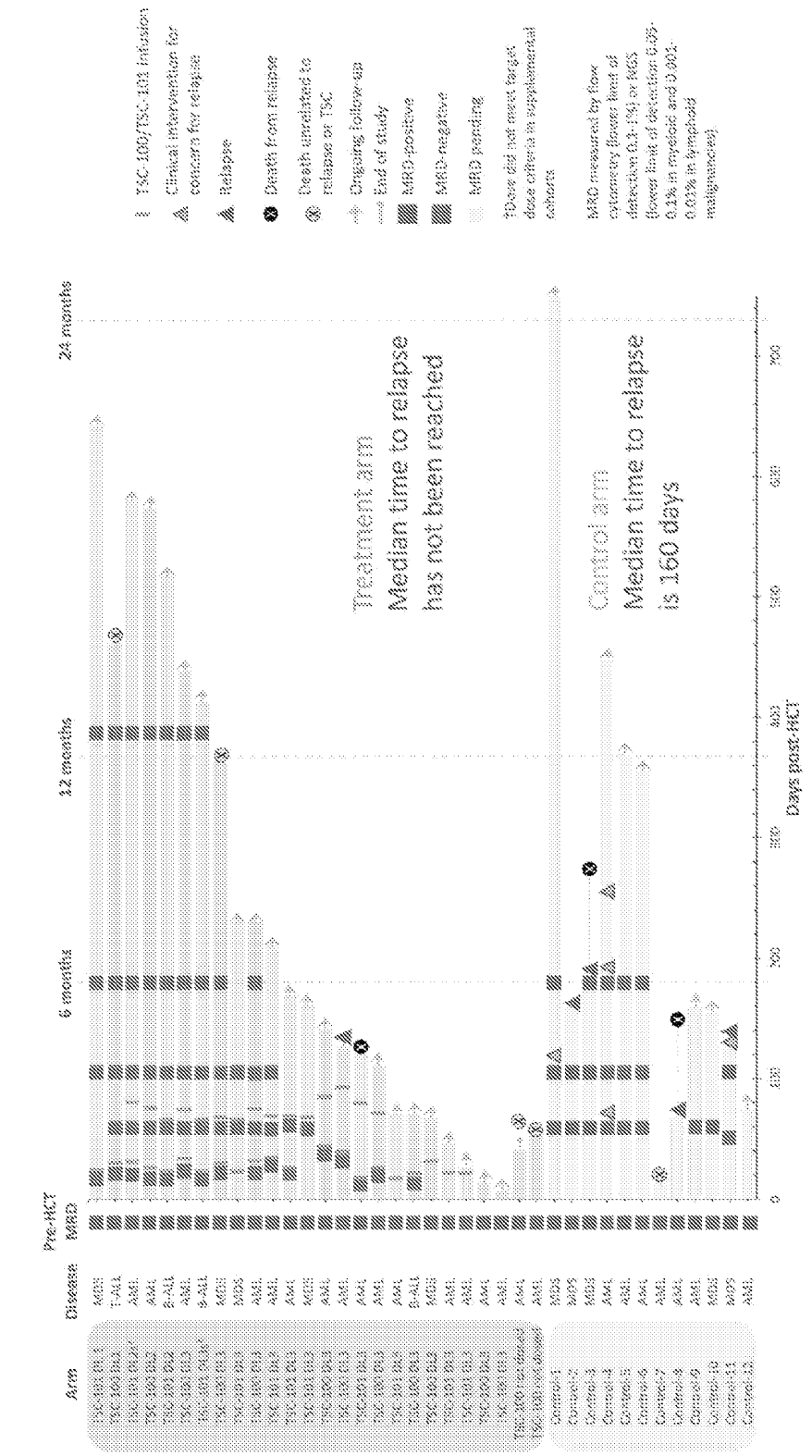

Arm
Disease
Pre-HCT MRD
6 months
12 months
24 months
0
180
360
540
720
900
Days post-HCT
Treatment arm
Median time to relapse
has not been reached
Control arm
Median time to relapse
is 160 days
TSC-100/TSC-101 infusion
Clinical intervention for concern for relapse
Relapse
Death from relapse
Death unrelated to relapse or TSC
Ongoing follow-up
End of study
MRD-positive
MRD-negative
MRD pending
Dose did not meet target dose criteria in supplemental cohorts
MRD measured by flow cytometry (lower limit of detection 0.1% or NGS (lower limit of detection 0.05-0.1% in myeloid and 0.001-0.01% in lymphoid malignancies)

FIG. 34

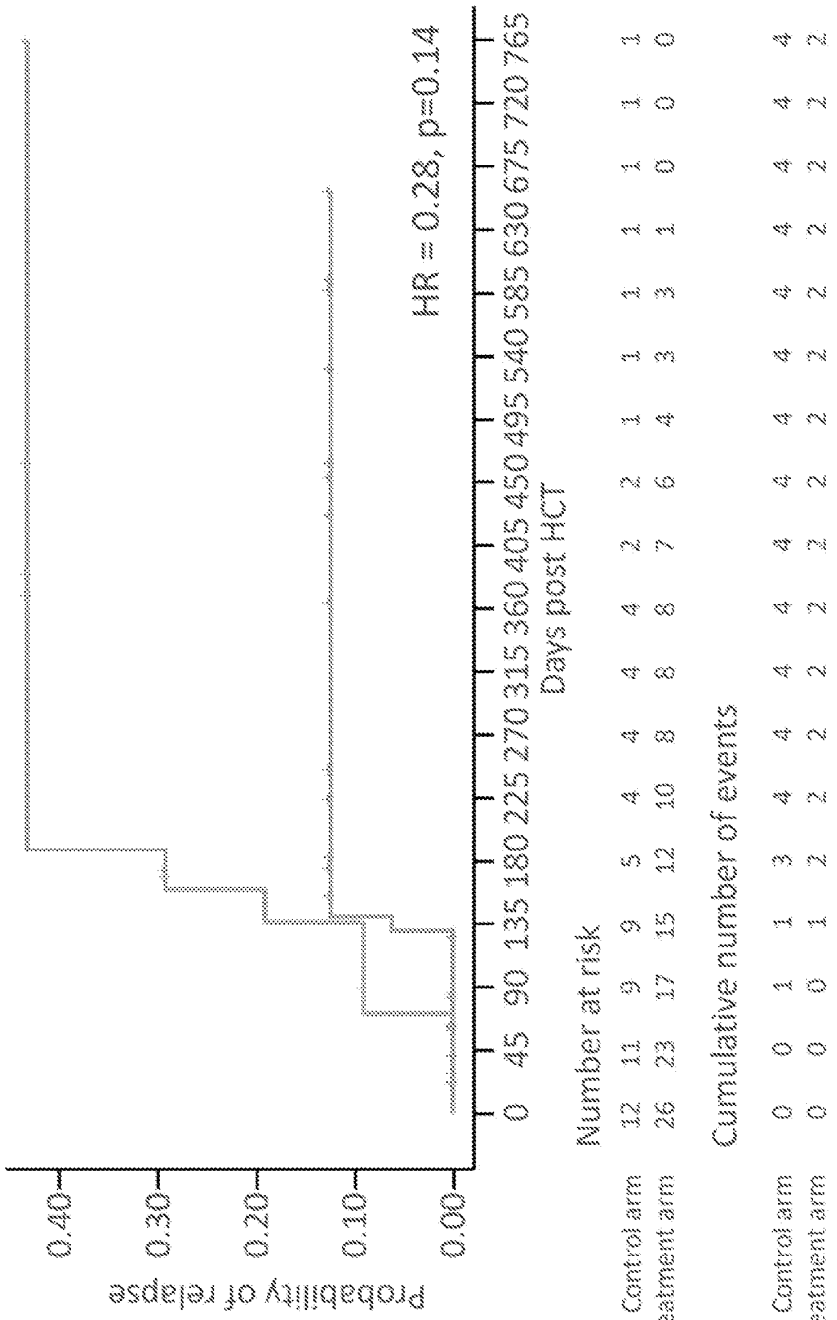
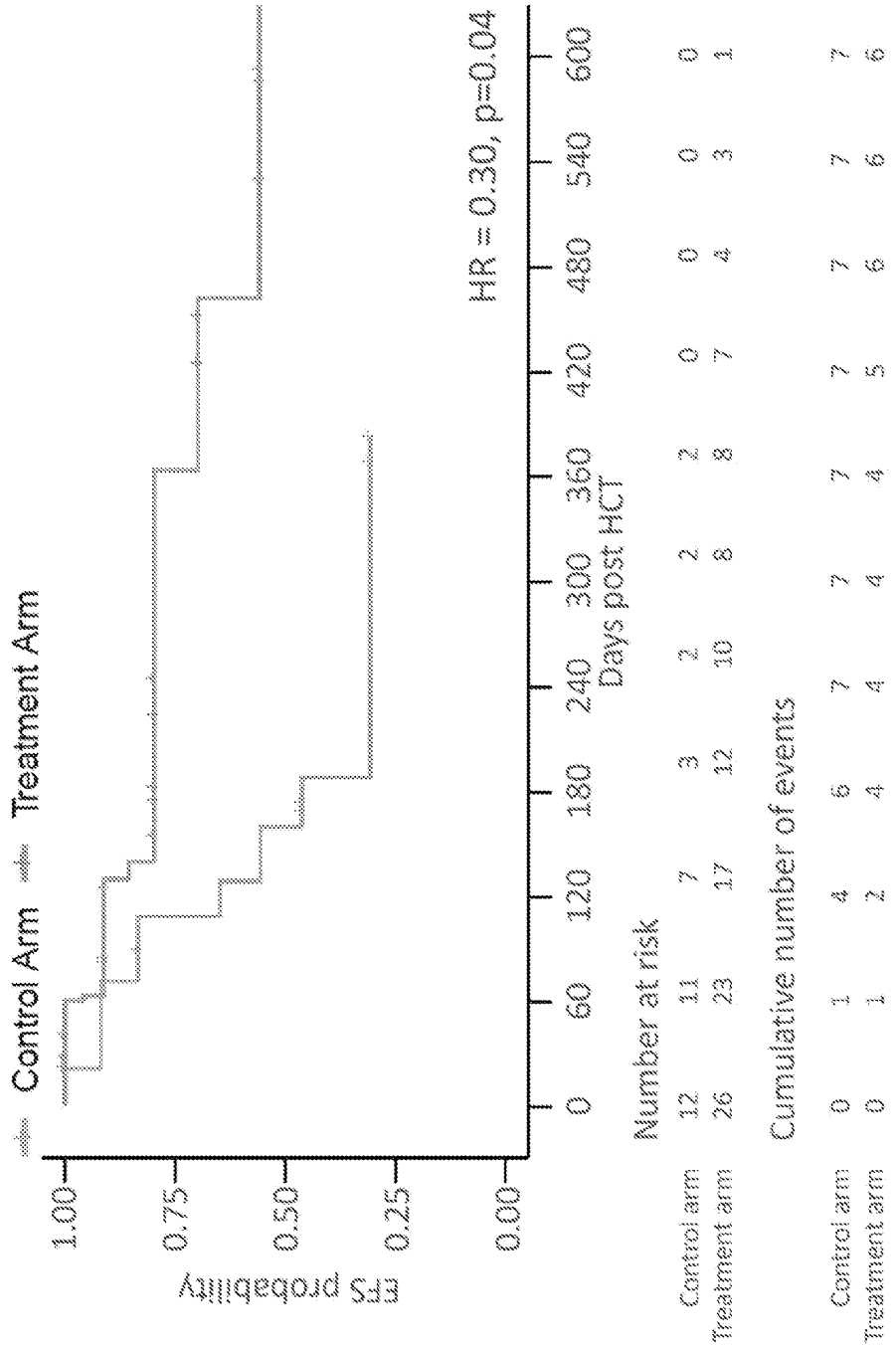

Control Arm
Treatment Arm
Probability of relapse
0.40
0.30
0.20
0.10
0.00
HR = 0.28, p=0.14
0 45 90 135 180 225 270 315 360 405 450 495 540 585 630 675 720 765
Days post HCT
Number at risk
Control arm 12 11 9 9 5 4 4 4 2 2 1 1 1 1 1 1 1
Treatment arm 26 23 17 15 12 10 8 8 7 6 4 3 3 1 0 0 0
Cumulative number of events
Control arm 0 0 1 1 3 4 4 4 4 4 4 4 4 4 4 4 4
Treatment arm 0 0 0 1 2 2 2 2 2 2 2 2 2 2 2 2 2

FIG. 35


Control Arm
Treatment Arm
EFS probability
1.00
0.75
0.50
0.25
0.00
HR = 0.30, p=0.04
0 60 120 180 240 300 360 420 480 540 600
Days post HCT
Number at risk
Control arm 12 11 7 3 2 2 2 0 0 0 0
Treatment arm 26 23 17 12 10 8 8 7 4 3 1
Cumulative number of events
Control arm 0 1 4 6 7 7 7 7 7 7 7
Treatment arm 0 1 2 4 4 4 4 5 6 6 6

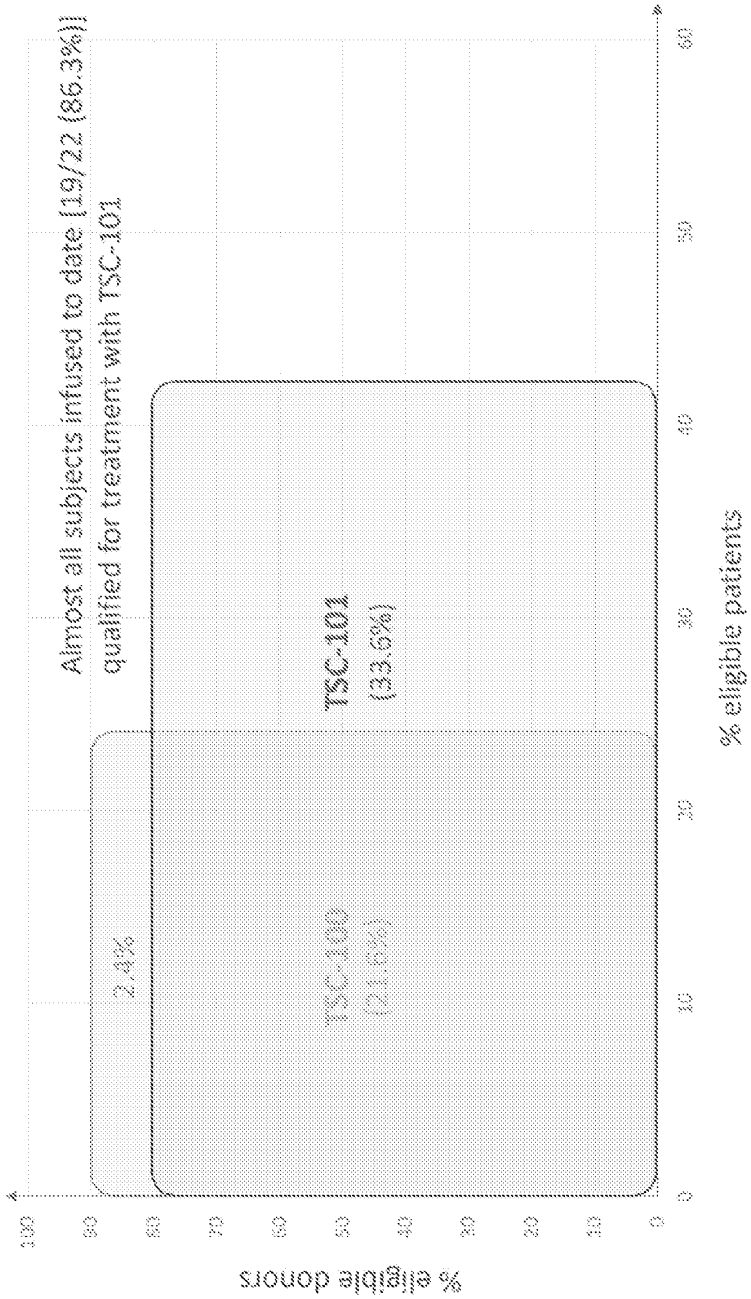

Almost all subjects infused to date [19/22 (86.3%)] qualified for treatment with TSC-101
2.4%
TSC-100
(21.6%)
TSC-101
(33.6%)
% eligible donors
% eligible patients
100
90
80
70
60
50
40
30
20
10
0

FIG. 36

FIG. 37

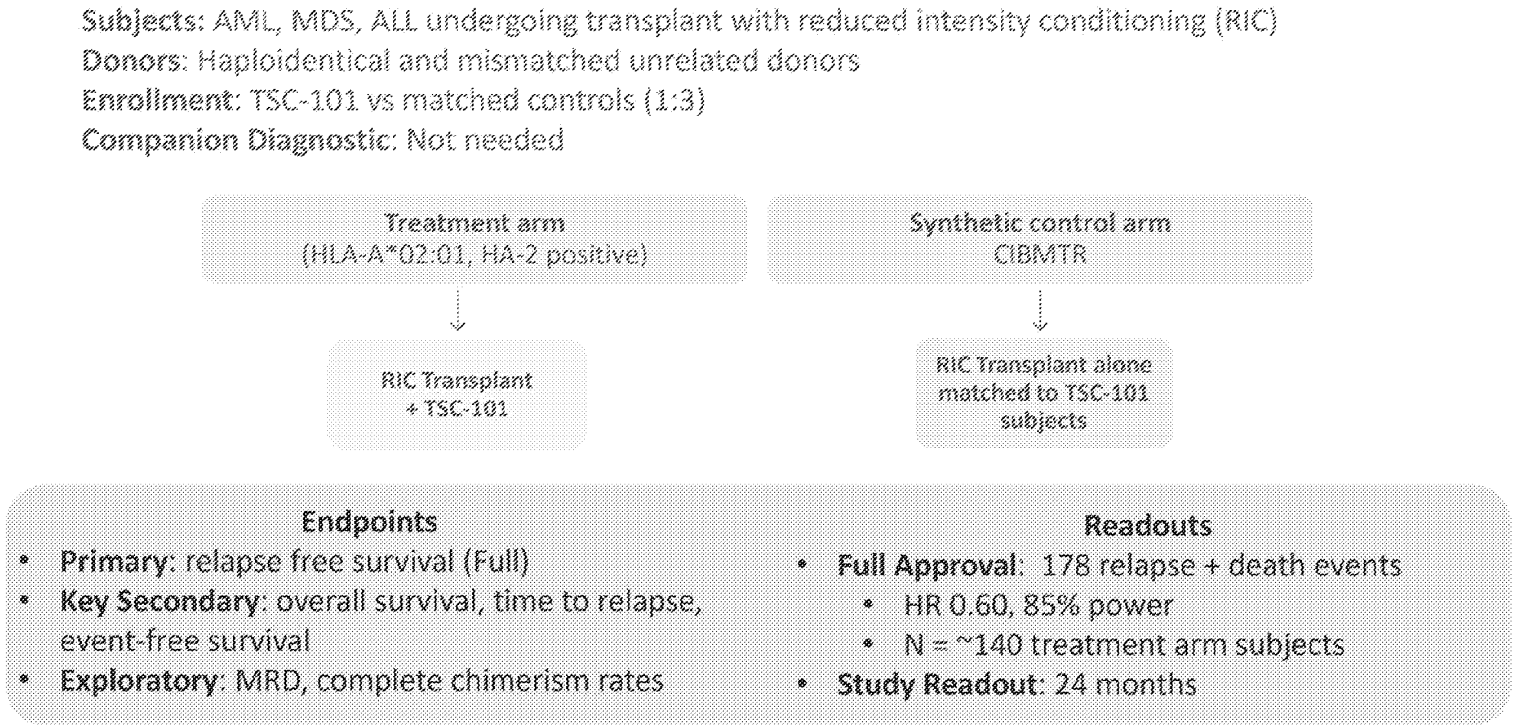

Subjects: AML, MDS, ALL undergoing transplant with reduced intensity conditioning (RIC)
Donors: Haploidentical and mismatched unrelated donors
Enrollment: TSC-101 vs matched controls (1:3)
Companion Diagnostic: Not needed
Treatment arm
(HLA-A*02:01, HA-2 positive)
Synthetic control arm
CIBMTR
RIC Transplant
+ TSC-101
RIC Transplant alone
matched to TSC-101
subjects
Endpoints
• **Primary**: relapse free survival (Full)
• **Key Secondary**: overall survival, time to relapse, event-free survival
• **Exploratory**: MRD, complete chimerism rates
Readouts
• **Full Approval**: 178 relapse + death events
• HR 0.60, 85% power
• N = ~140 treatment arm subjects
• **Study Readout**: 24 months

FIG. 38

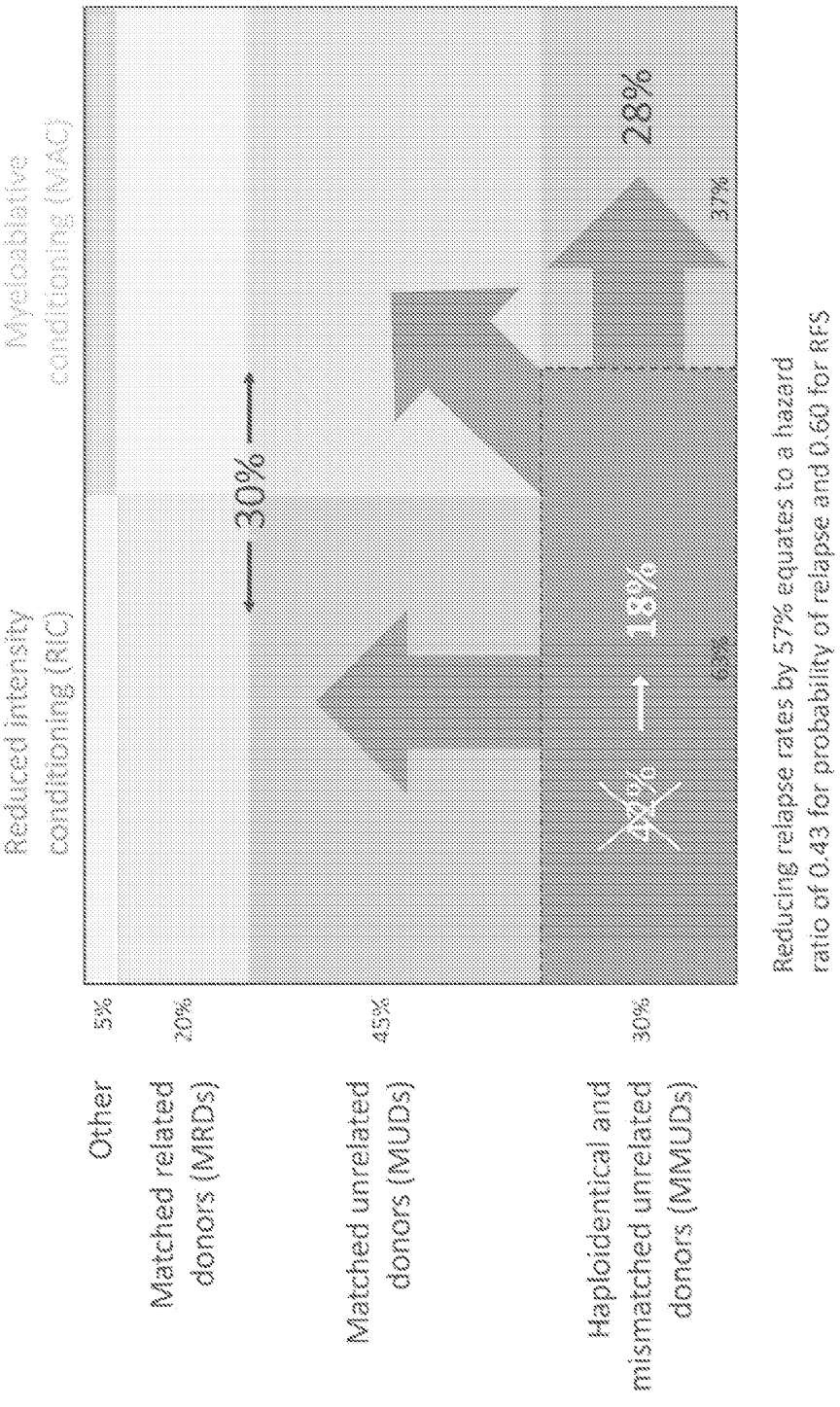

Reduced intensity conditioning (RIC)
Myeloablative conditioning (MAC)
30%
18%
28%
37%
Other
5%
Matched related donors (MRDs)
20%
Matched unrelated donors (MUDs)
45%
Haploidentical and mismatched unrelated donors (MMUDs)
30%
Reducing relapse rates by 57% equates to a hazard ratio of 0.43 for probability of relapse and 0.60 for RFS

FIG. 39

Dose Level	Planned Day of Infusion Post HCT	
	+21	+61
DL1	5×10^6 TCR-T cells/kg	N/A
DL2	5×10^6 TCR-T cells/kg	5×10^6 TCR-T cells/kg
DL3	5×10^6 TCR-T cells/kg	20×10^6 TCR-T cells/kg
DL4	0.8 billion cells	1.6 billion cells
DL4*	1.2 billion cells	1.2 billion cells