Phase 1 trial of TSC-100 and TSC-101, Engineered T-Cell Therapies Targeting Minor Histocompatibility Antigens to Eliminate Residual Disease after Hematopoietic Cell Transplantation

Moniz Al Malik1, Alla Keyzner2, Hyung C. Suh3, Aasiya Matin4, Erica Buonomo5, Yun Wang6, Nina Abelowitz5, Jim Murray5, Gavin MacBeath5, Deborah Barton6, Shrikanta Chattopadhyay5, Ran Reshef6, City of Hope Medical Center, Duarte CA. 2 Mount Sinai Hospital, New York NY, 3 Hackensack University Medical Center, 4 Karmanos Cancer Institute, Detroit MI, 5 TScan Therapeutics, Waltham MA. 6 Columbia University Medical Center, New York NY

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Introduction 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 mismatched between transplant recipients and 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 hematopoietic cells while leaving donor hematopoietic cells untouched.

Inclusion/Exclusion Criteria and Key Specifications for Study NCT05473910

Inclusion Criteria
- Patients in all arms:
  - ≥18 years with AML, ALL or MDS
  - Conversion from MRD positive to TScan
  - Control arm: Any HLA type apart from Fludarabine/melphalan/thiotepa
- Post any therapy per institutional
- Donors for TScan: Ha1 and Ha2
- Prior allogeneic HCT

Exclusion Criteria
- Patients in all arms:
  - Levels of donor-specific HA-antibodies high enough to warrant desensitization protocols and who have no alternate donors
  - Treatment arm: 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)

Protocol Specifications

- RIC regimens:
  - Fludarabine/cyclophosphamide total body irradiation (200 or 400 cGy)
  - Fludarabine/melphalan/thiotepa (200 cGy)
  - Thiotepa/melphalan/thiotepa
- GVHD prophylaxis:
  - Post-transplant cyclophosphamide (Days 3, 4)
  - Mycophenolate (until Day 26)
  - Tacrolimus (until Day 30)

Acute or chronic GVHD treatment:
- Any therapy per institutional guidelines

Maintenance therapies:
- FLT3, BCRA2, DH in 11 patients allowed 60 days post TSC-101 or after Day 100
- Other ant-leukemia agents (e.g., oral azacitidine) not allowed

Investigational Exploratory 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
- Post-transplant MRD+ patients have ~67% risk of relapse with RIC.

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

Mixed donor cell chimerism
- Standard STR-based assay
- Prog: clinically validated: measurable in all patients; mixed chimerism predicts ~50% risk of relapse
- Poor: Limit of detection (~1%); PTCy causes high donor chimerism > 98% by Day 30
- Novel NGS-based assay (AlloHeme)
- Prog: NGS of ~400 SNPs improves limit of detection to 0.13%
- Corr: Predictive value of NGS assay unknown, trial ongoing (NCT04635384)

Chimerism detection approach
- Donor chimerism confirmed in bone marrow, whole blood, CD3 and CD33 subsets using standard STR and novel NGS
- 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-101 persistence in the treatment arms. Following transplantation, residual HA-positive patient derived malignant cells are measured with high sensitivity on MRD assays (left) whereas residual HA-positive patient derived hematologic malignancies, malignant, pre-malignant or normal, are measured using standard and high-sensitive techniques. 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 ASISGT, May 2023.

References:
8. Al Malik M et al. Mol Ther, 2023, 31 (Supplement 1): S1-794