Histocompatibility Antigens to Eliminate Residual Disease After Hematopoietic Cell Transplantation

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

Monzr M. Al Malki1*, Hyung C. Suh2, Alla Keyzner3, Aasiya Matin4, Yun Wang5, Nina Abelowitz5, Jim Murray5, Gavin MacBeath5, Debora Barton5, Shrikanta Chattopadhyay5, Ran Reshef6

1*Presenting author; 1City of Hope, Duarte, CA, Hackensack Medical Center, Hackensack, NJ, 2Mount Sinai, New York, NY, 3Karmanos Cancer Institute, Detroit, MA, 4TScan Therapeutics, Waltham, MA, 5Columbia University, New York, NY

Background and Rationale

Myeloid malignancies such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and certain acute lymphoblastic leukemias (ALL) have 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 (MHAs) mismatched between patients and donors.

The TScan-001 trial is studying TCR-Ts engineered to target MHAs, HA-1 (TSC-100) or HA-2 (TSC-101) to eliminate residual blood cell populations post-HCT, thereby sparing normal blood cell populations.

Donor hematopoietic cells negative for MHAs or HLA-A*02:01 are used to perform HCT, thereby sparing normal blood cells post-HCT.

Patients have been enrolled into all three arms of the study:

- TSC-101: HA-1+ patients (60%)
- TSC-100: HA-2+ patients (40%)
- Control: HA-1−/2− patients

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

- Adverse events: N=1,356
- SAEs: N=1,356

In the TSC-101 and TSC-100 arms, adverse events and SAEs were not significantly different from the control arm.

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

TP53 mutant MDS patient treated from MRD(+) to MRD(-) after HCT & TSC-101

TP53 mutated MDS has ~80% risk of relapse or death after HCT (Lindsey 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).

Patients with positive TP53 mutations at HCT have a high risk of relapse, defined here as UD (detectable) chimerism at the end of the first year following HCT.

Conclusions:

- The TScan Platform is safe and tolerable.
- We have demonstrated preliminary efficacy in reducing residual disease.
- There is a potential role for TCR-Ts targeting MHAs in the field of hematopoietic cell transplantation.

References:

- Liu et al., J Biopharm Stat., 2020
- Monzr M. Al Malki1*, Hyung C. Suh2, Alla Keyzner3, Aasiya Matin4, Yun Wang5, Nina Abelowitz5, Jim Murray5, Gavin MacBeath5, Debora Barton5, Shrikanta Chattopadhyay5, Ran Reshef6
- Lindsley et al., NEJM 2017
- Craddock, J Clin Oncol 2021

Multicenter Trials

- 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)