Trial in Progress: A Phase 1 Umbrella Study of TCR-Engineered T Cells That Target HA-1 (TSC-100) and HA-2 (TSC-101) to Treat Residual Leukemia after Hematopoietic Cell Transplantation

Introduction

Engineered T cell therapies targeting the lineage-specific antigens CD19 (B cells) or BCMA (plasma cells) are highly effective in patients with lymphoid malignancies and feasible because depleting normal B cells or plasma cells can be tolerated by patients. Targeting lineage antigens on myeloid malignancies is not feasible, however, since depleting normal myeloid cells like neutrophils would lead to serious complications such as sepsis neutropenia. To address myeloid malignancies with T cell therapies, one solution is to target antigens that are expressed on the hematopoietic cells of patients undergoing allogeneic hematopoietic cell transplantation (HCT), but not expressed on their donor’s cells. Hematopoietic lineage-specific minor histocompatibility antigens (MiHAs) can be presented on the cell surface by human leukocyte antigens (HLA). TScan has developed the engineered T cell products TSC-100 and TSC-101 that express TCRs to specific minor histocompatibility antigens (MiHAs) that are expressed on their donor’s cells. These products are engineered to eliminate all recipient hematopoietic cells while leaving donor hematopoietic cells untouched. These products are being developed in patients with AML, ALL and MDS undergoing HCT to eliminate any residual hematopoietic cells after HCT and prevent disease relapse that affects ~40% of patients. We describe the clinical trial design and translational assays to generate early evidence of biological activity.

Product characteristics: TMC modifications, CD34 tag, CD8β/γ coreceptors

The common vector used to manufacture TSC-100 or TSC-101 includes a strong promoter, modifications to ensure correct TCR pairing, a CD34 tag to purify and track the engineered T cells, and CD8β/γ coreceptors to allow CD4+ helper T cells to participate in target recognition and cytokinetics. The manufacturing platform uses a transposon transposase system enabling the introduction of larger vectors with an increased number of functional elements.

Overall trial design for TSC-100/ TSC-101 in patients undergoing HCT

Patients with AML, MDS and ALL planned for HCT with reduced intensity conditioning (RIC) from a haploidentical donor (haplo) are assigned to treatment or control arms dependent on their HLA and minor antigen type. All patients must be HLA-A*02:01 positive for assignment to treatment arms. If they are HA-1 positive (~60% prevalence), they receive TSC-100 with standard of care (SOC) transplantation. If HA-2 positive (40%) they receive TSC-101 + SOCT. Donors would need to be mismatched for either HLA or minor antigen type. Patients without HLA-A*02:01 (~40%) or without mismatched donors will be assigned to the SOC control arm.

Inclusion/ exclusion criteria and key protocol restrictions

Exclusion Criteria

- Patients in all arms: 
  - Lymphoblastic leukemia
  - ECOG PS ≥3
  - History of severe or persistent renal impairment (eGFR ≤30 ml/min/1.73 m²)
  - Severe uncontrolled hypertension (systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg)
  - Age <18 or >65 years
- Patients in TSC-100 arm: 
  - 3+12 patients with HLA-A*02:01 positive
  - Donors matched to TSC-101 participants should be negative for HLA-A*02:01 alleles

Donors in treatment arms:

- Able to undergo peripheral blood stem cell (PBSC) collection and 2 rounds of leukapheresis
- Donors matched to TSC-100 participants should be negative for HLA-A*02:01 alleles

TSC-100 or TSC-101 target HA-1 (A) or HA-2 (B) was measured using peptide-pulsed T2 cells.

Potency of TSC-100 or TSC-101 targeting HA-1 (A) or HA-2 (B) is a measure of biological activity.

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

Donors for patients in treatment arms will undergo 2 rounds of leukapheresis. The first is before G-CSF mobilization and is used to manufacture TSC-100/101. The second is after G-CSF mobilization and is for standard peripheral blood stem cell (PBSC) collection.

Patients will undergo standard RIC conditioning followed by stem cell infusion then post-transplant cyclophosphamide (PTCy). Upon count recovery (around Day 21), they will receive a single dose of TSC-100 or TSC-101 (TSC-10X) in Dose Level 1. In Dose Level 2, patients receive 2 doses of TSC-10X around Day 21 and the second 40 days after the first dose (around Day 61). In Dose Level 3, the second dose will be escalated to 4X the initial dose. Dose escalation will follow interval 3+3 design (3+3) with 3-12 patients per cohort.

Endpoints: Primary endpoints include adverse event profile and dose limiting toxicities. Secondary endpoints include relapse rates at 1 year. Exploratory endpoints include donor chimerism kinetics, MRD+ rates & TSC-10X persistence.

Early markers of efficacy and biological activity in translational labs

Minimal Residual Disease (MRD)

Pre-transplant

- Combination of next-generation sequencing (NGS) with flow cytometry detects MRD in 40% of AML patients

Post-transplant

- MRD detection: 
  - Patients treated with TSC-100/101 have ≥87% risk of relapse with RIC

MRD detection approach

- NGS assays: 
  - Pros: increased sensitivity, better MRD detection limit of detection of 0.04%
  - Cons: high cost and time to obtain results

Chimerism detection approach

- Standard STR-based assay
  - Pros: low cost and time to obtain results
  - Cons: high detection limit

- Novel NGS-based Assay (Altimmune)
  - Pros: NGS of ~400 SNPs improves limit of detection of 0.04%
  - Cons: high cost and time to obtain results

- Mixed donor cell chimerism

- Standard STR-based assay
  - Pros: clinically validated, measurable in all patients; mixed chimerism predicts ~60% risk of relapse

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References