STEADFAST: A First-in-Human Study Assessing HLA-A*02-Chimeric Antigen Receptor Regulatory T Cells in Renal Transplantation

Abstract #798
Board No. TU-303

Katharina Schreeb, MD, MBA,[1] Ben Hsu ,MD, PhD,[2] Celine Dumont, PhD,[1] Gill Atkinson, PhD,[1] Emily Culme-Seymour,PhD,[1] Petra Reinke, Md, PhD,[3]

[1]Sangamo Therapeutics France, Allée de la Nertière, Les Cardoulines HT1, 06560 VALBONNE, France; [2]Sangamo Therapeutics, 7000 Marina Blvd, Brisbane, CA; [3]Charité Universitätsmedizin Berlin, Berlin, Germany

Introduction

- Renal transplantation is a lifesaving therapy for patients with end-stage renal disease (ESRD) but requires lifelong immunosuppressive treatment to prevent rejection of the graft
- Immunosuppressive therapy is frequently associated with adverse effects, as it has a high risk of severe infections, cardiovascular disease, and malignancy, which comprise the 3 leading causes of death in transplant recipients.[1] Therefore, an important goal in transplantation medicine is the creation of immune tolerance aiming at allograft acceptance while enabling reduction of immunosuppressive therapy
- Regulatory T cells (Tregs) are key mediators of immune tolerance and maintain immune homeostasis. Antigen-specific Tregs are reported to be more potent than polyclonal Tregs.[2] Following antigenic stimulation, Tregs are expected to be recruited to the allograft and activated to exert their immunosuppressive function, including suppression of effector T cell (Teff) expansion and activity
- Mismatched human leucocyte antigens (HLAs) between donor and graft recipients are a major barrier to successful transplantation, as HLA molecules elicit strong immune responses and generation of anti-donor HLA antibodies, which can lead to frequent rejection episodes. HLA class I molecule A*02 (HLA-A*02) has a high allelic frequency
  - Approximately 70% of White transplant recipients are HLA-A*02 negative and 30% of organ donors are HLA-A*02 positive, leading to a potential mismatch in 21% to 26% of transplantations[3,4]

Investigational Product

- TX200-TR101 is a cell therapy consisting of ex vivo expanded autologous naive regulatory T cells genetically modified to express a chimeric antigen receptor (CAR) specific to the mismatched donor HLA-A*02 antigen on their surface membrane
- The CAR is composed of a single-chain variable fragment from a humanized antibody that recognizes the HLA-A*02 antigen, coupled to a transmembrane domain and the activation domain of human CD28 and human CD3 zeta
- The lentiviral vector carrying the CAR construct used for the transduction of the Tregs is based on a third-generation, self-inactivating lentiviral vector

Preclinical Results

- HLA-A*02 CAR-Tregs (TX200-TR101) can be specifically activated through their HLA-A*02 CAR, exert antigen-specific suppression, proliferate in vitro, and maintain a stable (functional) phenotype
- In vivo mouse model data provided evidence that TX200-TR101 was able to efficiently inhibit human peripheral blood mononuclear cell engraftment as well as onset of graft-versus-host disease in NSG mice[5]
- TX200-TR101 was also able to release immune-modulatory cytokines, which should facilitate establishment of immune tolerance

First-in-Human Clinical Trial Design

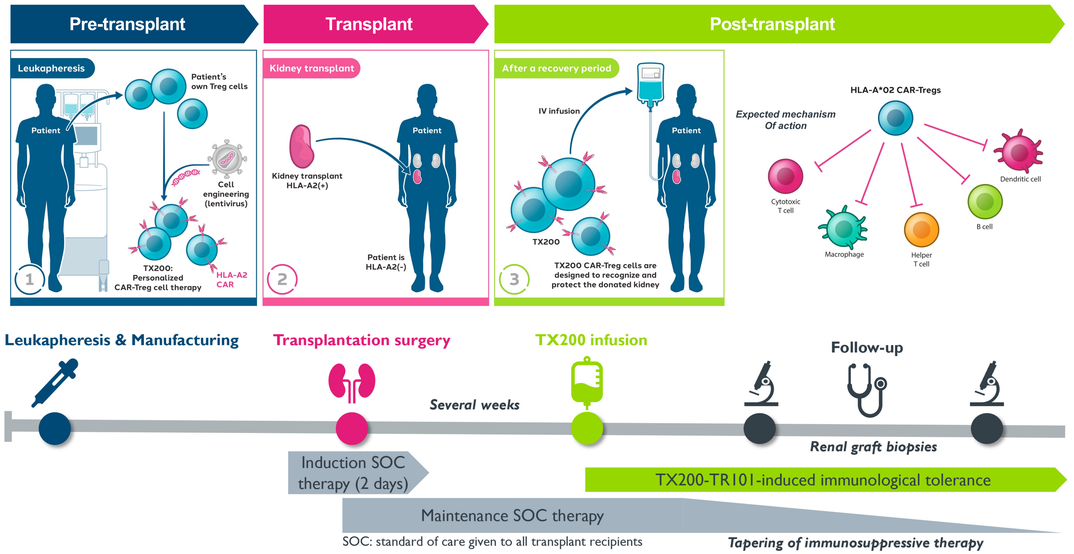
- In this first-in-human (FIH) phase 1/2 study, HLA-A*02–negative patients with ESRD awaiting a kidney graft from an HLA-A*02–positive living donor will undergo leukapheresis to collect autologous Tregs for the manufacture of TX200-TR101 CAR-Tregs
- Several weeks after transplantation, TX200-TR101 will be administered via a single intravenous infusion. We plan to test 3 weight-adjusted doses of TX200-TR101 in single-dose, ascending-dose cohorts
- A small control cohort of HLA-mismatched transplant recipients with similar immunological risk also will be recruited
- All transplant recipients will be followed up for 84 weeks post-transplant in the STEADFAST study
  - In addition, transplant recipients will have the opportunity to enter a separate study to be followed up for 15 years after TX200-TR101 administration according to regulatory guidelines for genetically modified cell therapy products

Objectives/Endpoints

Primary objective: Safety and tolerability of TX200-TR101

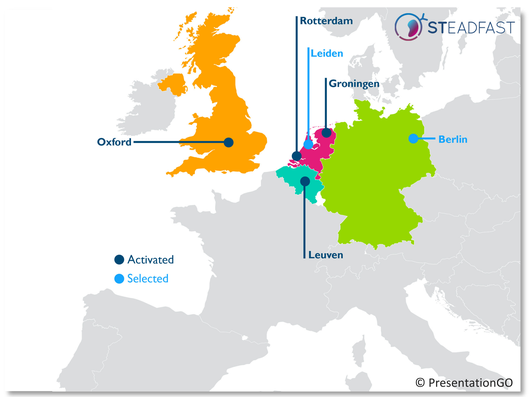
Primary endpoint: Incidence and severity of treatment-emergent adverse events within 28 days post–TX200-TR101 infusion

- Other endpoints include additional safety parameters as well as clinical and renal outcome parameters, with endpoints regarding graft dysfunction or rejection based on established diagnostic methods including biopsies at prespecified timepoints
- The evaluation of a range of biomarkers will determine the localization of TX200-TR101 in the graft and the effects on graft and peripheral immune responses



Study status as of April 30, 2022

Site Activation Metrics	Total	BEL	GER	NDL	UK
Sites Selected	6	1	1	3	1
Sites Activated	4	1	0	2	1



- **The first transplant patient was dosed with TX200 TR101 in March 2022.** To date, the treatment has been well tolerated, and no post-treatment adverse events have been reported.

Summary

- TX200-TR101 holds great promise to prevent immune-mediated graft rejection and induce immunological tolerance following HLA-A*02–mismatched renal transplantation
- It is anticipated that induced immune tolerance would enable reduction of immunosuppressive therapy while maintaining allograft acceptance
- This FIH study provided the setting for the first-ever dosing of a human with a CAR-Treg investigational cell therapy

References

1. Katabathina V, et al. *Radiol Clin North Am*. 2016;54(2):303-319.
2. Duggleby R, et al. *Front Immunol*. 2018;9:252.
3. González-Galarza FF, et al. *Nucleic Acids Res*. 2015;43(Database issue):D784-D788.
4. Noyan F, et al. *Am J Transplant*. 2017;17(4):917-930.
5. Proics E, et al. Preclinical assessment of antigen-specific chimeric antigen receptor regulatory Tcells for use in solid organ transplantations. Unpublished data, 2022.

Author Disclosures

Dr Reinke reports grants from EU, and grants from BMBF. All other authors are employees of Sangamo Therapeutics.

Contact: Katharina Schreeb kschreeb@sangamo.com

Presented at the ASGCT 25th Annual Meeting, 2022