A phase 1, first in human, open-label, dose escalation and dose expansion study of TST005 in patients with locally advanced or metastatic solid

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Abstract TIP 771

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Background

Anti-programmed death 1 / ligand 1 (PD-1/PD-L1) therapies have been established as standard treatment for multiple tumor types. However, the key challenge of these therapies is resistance caused by immunosuppressive factors in the tumor microenvironment (TME). TGF-β is a multi-functional cytokine that is involved in the tight regulation of either antitumor immunity or tumor immunosuppression. TGF-β promotes an immune exclusion TME thus renders PD-L1 blockade ineffective. Therefore, dual targeting PD-L1 and TGF-β represents a rational synergistic strategy to enhance clinical outcome relative to each agent alone.

TST005 is a novel bi-functional fusion protein combining a high affinity PD-L1 monoclonal antibody (mAb) in a fragment crystallizable (Fc) silenced immunoglobulin G1 (IgG1) backbone and a differentiated transforming growth factor beta (TGF-β) trap with improved stability. This study will investigate TST005's safety, tolerability and preliminary anti-tumor activity in solid tumors.

Pre-Clinical Data

TST005 inhibits tumor growth in the mouse models

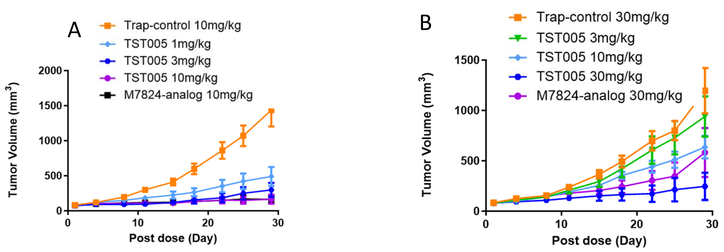


Figure 1. Tumor growth curve of TST005 and M7824 analog (mean± S.E.M, n=10). A. In the MC38/hPD-L1 colorectal tumor model, At 10mg/kg, TST005 showed similar tumor inhibition compared to M7824 analog. B. In the EMT6/hPD-L1 breast tumor model, a model with higher TGF-β expression, at 30 mg/kg TST005 treatment showed better tumor inhibition compared to M7824 analog.

TST005 depletes plasma and tumor TGF-β1 in mouse model

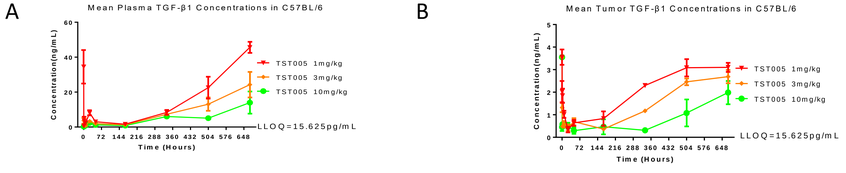
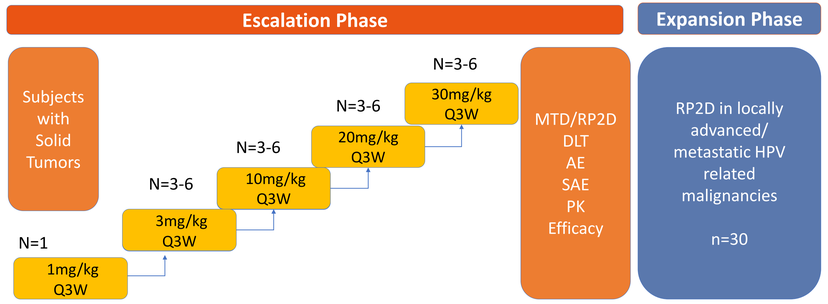


Figure 2. The concentration of TGF-β1 in the MC38/hPD-L1 tumor–bearing mice treated with TST005 via single IV injection. Plasma (A) and tumor (B) TGF-β1 concentration were analyzed at pre-dose and 30min, 2h, 8h, 24h, 48h, D7 and D14, D21, D28 after treatment. TGF-β1 depletion in both plasma and tumor tissue was showed in a dose dependent manner with maximum depletion at 10mg/kg.

Methods and Study Design

TST005-1001 (NCT04958434) is a phase 1, first in human (FIH) open-label, multicenter trial that consists of a dose escalation phase in patients with advanced solid tumors who have failed prior therapy and a dose escalation phase in human papillomavirus (HPV) related malignancies not amenable to surgery and who have received prior standard therapy(ies).

Study Schema



Dose escalation phase

Comprises five dose cohorts: accelerated titration of 1 subject in the starting dose cohort (1 mg/kg), and then four dose cohorts (3 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg) following classic 3+3 design. No more than one prior immune checkpoint inhibitor (ICI) treatment is allowed for eligible subjects.

Dose expansion phase

Up to 30 patients with locally advanced or metastatic HPV+ malignancies, including cervical cancers, P16+ Oropharyngeal cancers, and other tumors that are known HPV+, and who are ICI treatment naive will be enrolled to receive the recommended dose of TST005 treatment.

Treatment

For both phases, subjects will receive TST005 intravenous infusion every 3 weeks (Q3W) until disease progression per RECIST v1.1 and/or immune RECIST or unacceptable toxicity. Subjects may continue to receive TST005 beyond RECIST v1.1 defined progression, per iRECIST, at the discretion of the Investigator.

Objectives

Dose escalation phase

Primary:

- To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose(s) (RP2D) of TST005 in subjects with previously treated advanced solid tumors

Secondary:

- To characterize PK profile of TST005 in subjects with previously treated advanced solid tumors
- To characterize the immunogenicity of TST005

Dose expansion phase

Primary:

- To evaluate safety and tolerability of TST005 in subjects with locally advanced or metastatic HPV related malignancies

Secondary:

- To assess the efficacy of TST005 in subjects with locally advanced or metastatic HPV related malignancies by RECIST V1.1
- Additional safety and tolerability
- To assess the PK of TST005 in subjects with locally advanced or metastatic HPV related malignancies

Exploratory (Both Phases)

- To assess the efficacy of TST005 by iRECIST and RECIST V1.1 (escalation phase)
- To evaluate changes in disease biomarkers following treatment
- To explore correlations between biomarker expression, PK, PD and clinical readouts of TST005

Major Eligibility Criteria

Inclusion Criteria

- Male or female patients aged 18 years or older.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Adequate organ function per screening labs performed within 7 days of 1st dose

Dose escalation phase:

- Histologically or cytologically confirmed locally advanced or metastatic solid tumors.
- Tumor progression during or after prior therapy and for whom no standard therapy exists that would confer clinical benefit.
- Evaluable disease per RECIST v1.1

Dose expansion phase:

- Histologically or cytologically confirmed diagnosis of locally advanced or metastatic HPV+ malignancies, including cervical cancers, P16+ Oropharyngeal cancers, anal cancers, vulvar, vaginal, penile, and squamous cell rectal cancers and other solid tumors (e.g., lung, esophagus) that are known HPV positive.
- HPV related malignancy not amenable to potentially curative resection and have received prior standard of care therapy(ies) unless subject not eligible to receive standard therapy.
- At least 1 measurable lesion per RECIST v1.1

Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases.
- Active autoimmune diseases or history of autoimmune diseases that may relapse.

Dose Escalation phase

- More than one prior checkpoint inhibitor therapies (approved or investigational) in the advanced setting. One prior checkpoint inhibitor therapy is allowed

Dose Expansion phase

- Received any prior checkpoint inhibitor therapies (approved or investigational) in the advanced setting.
- Prior treatment with any therapy target TGF-β or TGF-β receptors pathway.

Study Status

This study is ongoing at 4 sites in the US and China. As of the 24 Aug 2022, the first three dose cohorts has been completed the evaluation and no DLT was observed. Clinical trial information: NCT04958434. Study Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

Abbreviations: AE = adverse event; DLT = dose limiting toxicity; HPV= human papillomavirus; MTD = maximum tolerated dose; PD = pharmacodynamics; PK = pharmacokinetics; Q3W = every 3 weeks; RP2D = recommended phase 2 dose; SAE = serious adverse event;