A first-in-human, open-label, multi-center phase 1 study of TST003, a GREM 1 inhibitor, in subjects with locally advanced or metastatic solid tumors

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Abstract 5977

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Background

Gremlin-1 (GREM1), a member of the TGF-β superfamily, plays a key role in EMT, and cancer cell proliferation by binding to BMPs. GREM1 is widely expressed in various human cancers and TME stromal cells. Overexpression of GREM1 is correlated with poor prognosis. TST003 is a novel humanized IgG1 monoclonal antibody targeting GREM1 with high affinity and selectivity, and it blocks GREM1 binding to BMP2/4 resulting in enhanced BMP signaling. This study will investigate TST003's safety, tolerability, and preliminary anti-tumor activity in patients with advanced solid tumors.

Pre-Clinical Data

TST003 Relieves BMP Signaling Inhibition Mediated by Gremlin-1

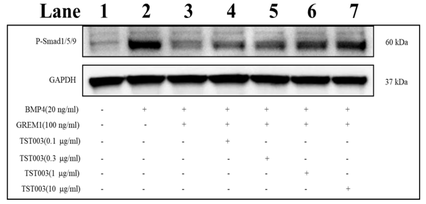
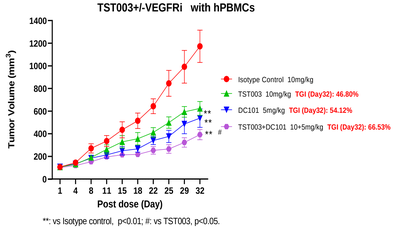


Figure 1. Seven groups were set in this experiment. 4*10^5 PC3 cells per well were plated in 12-well plates. BMP4 (20 ng/mL) as a positive group induced significant phosphorylation of Smad1/5/9, which was downstream of BMP signaling pathway. Gremlin-1 effectively inhibited p-Smad1/5/9 signal comparing with the positive and negative controls (Blank group). 0.1, 0.3, 1, 10 μg/mL of TST003 reversed Gremlin-1 inhibition and rescued the phosphorylation of smad1/5/9

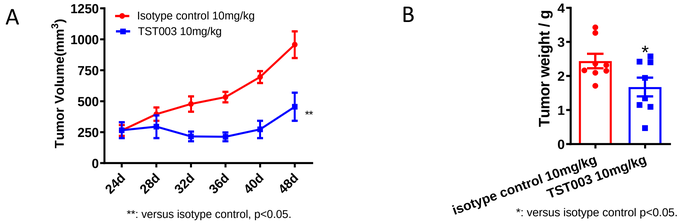
TST003 Displayed Single Agent and Combination Anti-Tumor Activity in MSS CRC PDX Tumor Model



**: vs Isotype control, p<0.01; #: vs TST003, p<0.05.

Figure 2. TST003 in vivo activities were evaluated using a colorectal cancer PDX tumor model (MSS, Kras G12D mutation and without PD-L1 expression) in humanized NOG mice reconstituted with human PBMC. Mice were randomized to 4 groups and administered with 10mg/kg isotype control, 10mg/kg DC101 (surrogate mouse anti-VEGFR-2) and 10mg/kg TST003, respectively. Mice were administrated with isotype control, DC101 and TST003 by *i.p* injection twice a week for 4 weeks. The results (B) indicated that 10mg/kg TST003 significantly inhibited tumor growth and had a better anti-tumor activity when combo with DC101.

TST003 Displayed Single Agent Anti-Tumor Activity in CRPC Tumor Model



**: versus isotype control, p<0.05.

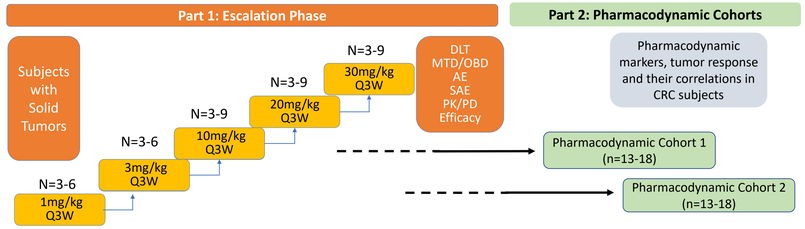
*: versus isotype control p<0.05.

Figure 3. CRPC PC3 cells were transplanted subcutaneously in nude mice. Nude mice were divided into 2 groups (N=8/group) and castrated after 12 days. TST003 and isotype control antibody were subsequently administrated every four days at 10 mg/kg for 3 weeks. Tumor volume (A) and tumor weight (B) were calculated every four days. As a result, 10 mg/kg TST003 exhibits significantly anti-tumor activity on prostate cancer PC3 xenograft tumor model on castrated male nude mice.

Methods and Study Design

TST003-1001 (NCT05731271) is a first in human Phase 1 study in locally advanced or metastatic solid tumor subjects having tumor progression during or after prior therapies and have no standard therapy that could confer clinical benefit.

Study Schema



Part 1: Dose escalation phase

Will evaluate sequential dose levels of TST003 *iv.*, every three weeks as a single agent.

Part 2: Pharmacodynamic cohorts

Will include 2 pharmacodynamic cohorts to evaluate the pharmacokinetic (PK) profile, pharmacodynamic (PD) markers, preliminary tumor response, as well as safety of TST003 as monotherapy in locally advanced or metastatic colorectal adenocarcinoma (CRC) subjects. The 2 doses used in the pharmacodynamic cohorts will be chosen from Part 1 and are expected to be within the pharmacologically active range based on nonclinical PK/PD modeling and available clinical PK/PD data from the ongoing study. Baseline GREM1 expression will be analyzed by immunohistochemistry. All subjects are required to undergo on-treatment tumor biopsy on cycle 3 day 1. In each pharmacodynamic cohort, around 13-18 subjects will be enrolled to ensure at least 7 GREM1 positive subjects.

Treatment

For both parts, subjects will receive TST003 intravenous infusion every 3 weeks (Q3W) until unacceptable toxicity or disease progression by RECIST v1.1. Subjects may continue TST003 treatment beyond RECIST v1.1 defined progression in the opinion of the Investigator after discussion with the Sponsor.

Objectives

Part 1: Dose escalation phase

Primary:
- To assess the safety and tolerability, and to determine the maximum tolerated dose (MTD) and/or optimal biologic dose (OBD) of TST003 as monotherapy in subjects with locally advanced or metastatic solid tumors

Secondary:
- To characterize PK profile of TST003 as monotherapy in subjects with locally advanced or metastatic solid tumors
- To characterize the immunogenicity of TST003 as monotherapy

Part 2: Pharmacodynamic cohorts

Primary:
- To assess PD markers, tumor response and their correlations with TST003 monotherapy in subjects with locally advanced or metastatic CRC

Secondary:
- To assess TST003 monotherapy anti-tumor activity, the safety profile and tolerability in subjects with locally advance or metastatic CRC
- To assess the PK profile of TST003 as monotherapy in subjects locally advanced or metastatic CRC
- To characterize the immunogenicity of TST003 as monotherapy

Exploratory objectives for both parts:

A comprehensive biomarker plan will be implemented to analyze GREM1 expression, BMP signaling pathway, and tumor microenvironment with tumor tissues (including tumor cells, CAFs, Teff, Treg, MDSCs and TAMs), as well as circulating tumor DNA :

- To demonstrate target engagement and assess tissue and blood-circulating biomarkers.
- To evaluate the correlation between drug exposure, pharmacodynamics and clinical outcomes.

Major Eligibility Criteria

Inclusion Criteria

- At least 18 years of age at the time of informed consent.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Adequate organ function per screening labs.
- Subjects who have tumor progression during or after prior therapy and for whom no standard therapy exists that would confer clinical benefit.

Part 1: Dose escalation phase:
- Subjects with histologically or cytologically diagnosed unresectable locally advanced or metastatic malignant solid tumors and who can provide archival tumor tissue that is formalin fixed and paraffin embedded (FFPE) for submission to central laboratory for biomarkers assessment..
- Tumor progression during or after prior therapies and for whom no standard therapy exists that would confer clinical benefit.
- Evaluable disease per RECIST v1.1

Part 2: Pharmacodynamic cohorts:
- Subjects with histological or cytological diagnosed unresectable locally advanced or metastatic colorectal adenocarcinoma. Biopsy at screening is strongly recommended though not mandatory. Archived tumor tissue as described above for Part1 (if no biopsy) at screening is mandatory. Subject must have tumor lesions accessible for on-treatment biopsy with acceptable risk per investigator's assessment.
- At least 1 measurable lesion per RECIST v1.1.

Exclusion Criteria

- Untreated or symptomatic central nervous system (CNS) metastases.
- Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, or targeted therapy or herbal medicine) within 4 weeks or 5 half lives (whichever is shorter) prior to the first dose of study drug.
- Severe interstitial lung disease, cardiovascular disease, intestinal disease, or other conditions.
- Active or uncontrolled infections of microbian.

Part 2: Pharmacodynamic cohorts:
- Prior treatment with an GREM1 targeted therapy. .
- Subject will not be able to undergo on-treatment tumor biopsy on cycle 3 day 1 per investigator best judgement as baseline.

Study Status

The enrollment is ongoing in clinical centers in the US and China. No significant safety signals were reported in the first few patients treated with TST003. Clinical trial information: NCT05731271. Study Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

Abbreviations: AE = adverse event; CRC = colorectal adenocarcinoma; CRPC = castration-resistant prostate cancer ; DLT = dose limiting toxicity; *iv.* = intravenous; MTD = maximum tolerated dose; OBD = optimal biologic dose; PD = pharmacodynamics; PK = pharmacokinetics; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event.