TPS476

A Multi-cohort Phase I/IIa Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of TST001 Administered as a Monotherapy, with Nivolumab or Standard of Care in Patients with Locally Advanced or Metastatic Solid Tumors (TranStar101/TST001-1001)

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BACKGROUND

- Gastric cancer (GC) remained the 4th leading cause of cancer death worldwide, accounting for about 7.7% of all cancer related mortality[1].
- Combinations of platinum and fluoropyrimidine are the preferred first-line chemotherapy regimen for patients with HER2 negative advanced gastric cancer[2]. Nivolumab was approved in combination with chemotherapy for first-line treatment of patients with advanced or metastatic gastric cancer. Though treatment outcome being improved, the median overall survival of nivolumab plus chemotherapy was still less than 14 months[3].
- Claudin-18 isoform 2 (CLDN18.2) is a member of the human claudin family of tetraspan membrane proteins that are crucial structural and functional components of tight junctions. CLDN18.2 expression is strictly limited to differentiated epithelial cells of gastric mucosa[5]. CLDN18.2 is ectopically expressed at a significant level in multiple tumor types including gastric, esophageal, pancreatic and lung cancers, making it an attractive anti-cancer target[5]. In G/GEJ cancer, its expression is independent from PD-L1[6].
- Zolbetuximab (IMAB362) is a clinical stage anti-CLDN18.2 antibody, significant improvement in PFS and OS was demonstrated when zolbetuximab was added to mFOLFOX6 or to CapOX as compared to placebo plus mFOLFOX6 or CapOx[4]. Results were limited to patients with CLDN 18.2 high expression (75%, 2+), which is about 38% of the population

Preclinical Data

- TST001 is a humanized IgG1 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC) activity via reduced fucosylation, and has stronger anti-tumor activities than IMAB362 analog, a chimeric anti-Claudin 18.2 antibody. (Figure 1)
- TST001 has shown a more potent complement mediated cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP) activities against CLDN18.2 expressing cells than IMAB362 analog.[7] (Figure 1B and C), may up regulate PDL1 expression.
- In vivo studies in mouse syngeneic tumor models demonstrated better efficacy of TST001 in low CLDN 18.2 expressors vs IMAB362 analog. (Figure 2A)
- The anti-tumor efficacy of triple combination of TST001 plus anti-PD-1 antibody and chemotherapy was significantly better than anti-PD-1 antibody in combination with chemotherapy or TST001 in combination with chemotherapy. (Figure 2B)

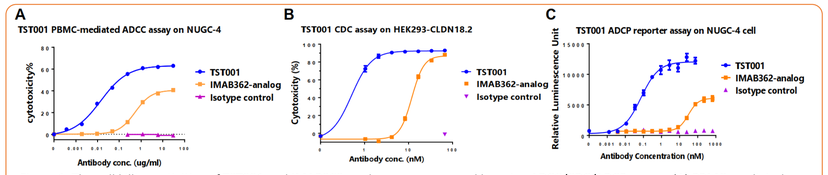


Figure 1. The cell killing activities of TST001 and IMAB362-analog were compared by using ADCC/CDC/ADCP assays. (A) PBMC-mediated ADCC assay. (B) CDC assay using human serum as complement and HEK293-CLDN18.2 as target cell. (C) ADCP reporter assay using NUGC-4 cell as target cell and Jurkat-NFAT-Luc-FcgRIIa cell as effector cell. The luminescence signal of effector cell indicates ADCP activity.

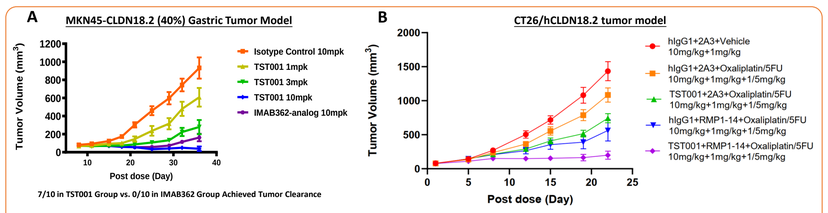


Figure 2. In vivo pharmacologic activity of TST001 monotherapy or in combinations in PDX tumor model.

Clinical Background

- TST001 combined with CAPOX as first-line treatment of patients with G/GEJ cancer is being explored in the Cohort C of study TranStar102.
- As of Aug 4th, 2022, 36 patients have been enrolled and treated with TST001 at 6mg/kg Q3W plus CAPOX in the expansion phase[8].
- Among the 15 patients with measurable disease and at least one post-treatment tumor assessment (Figure 3), 11 (73.3%) achieved partial response and 4 (26.7%) achieved stable disease as the best overall tumor response per RECIST1.1. Disease control rate is 100%[8].
- This cohort is still ongoing, updated data will be presented in another poster in this meeting.

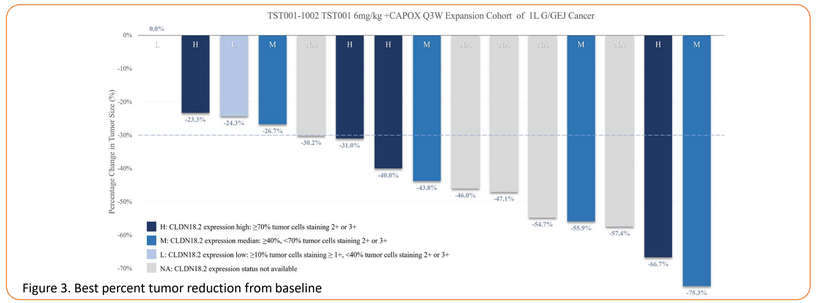
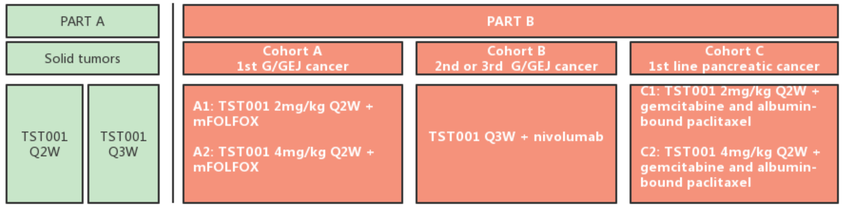


Figure 3. Best percent tumor reduction from baseline

METHOD

Study Design

- This is a phase I/IIa, open-label, multi-cohort, multi-center clinical study in US [NCT04396821]. Phase I (Part A) has been completed, and phase IIa (Part B) is ongoing.
- Patients with HER2 negative or unknown, untreated for locally advanced or metastatic G/GEJ adenocarcinoma will be eligible for Part B Cohort A to receive TST001 every two weeks combined with mFOLFOX6 plus nivolumab as the first-line treatment;
- Patients with G/GEJ adenocarcinoma who have failed one or two prior systemic therapies (prior nivolumab is allowed) will be eligible for Part B Cohort B to receive TST001 combined with nivolumab.
- Patients with advanced/metastatic pancreatic cancer will be eligible for Part B Cohort C to receive TST001 combined with gemcitabine, and nanoparticle albumin-bound paclitaxel every two weeks combined with mFOLFOX6 plus nivolumab as first-line treatment.
- Multiple doses and schedules will be assessed during Part B. (Figure 4)
- Each cohort consists of a safety run-in, then expansion phase.



Q2W = every 2 weeks; Q3W = every 3 weeks; FOLFOX = leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin

Primary Objectives

- To evaluate the safety and tolerability of TST001 single agent in patients with locally advanced or metastatic solid tumors
- To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of TST001 as monotherapy, in combination with nivolumab, in combination with nivolumab and mFOLFOX6, or in combination with gemcitabine and albumin-bound paclitaxel
- To evaluate the safety and tolerability of TST001 in combination with nivolumab in patients with locally advanced or metastatic GC/GEJ cancer.
- To evaluate the safety and tolerability of TST001 in combination with nivolumab and mFOLFOX6 in patients with locally advanced or metastatic GC/GEJ cancer.
- To evaluate the safety and tolerability of TST001 in combination with gemcitabine and albumin-bound paclitaxel in patients with locally advanced or metastatic pancreatic cancer.

Study Population

- Part A: solid tumor patients progressed after standard therapies, or intolerant of standard therapies, or with a tumor type without standard therapy.
- Part B Cohort A: about 15 patients with histologically or cytologically confirmed G/GEJ adenocarcinoma in each arm, who have not received prior systemic therapies for advanced disease
- Part B Cohort B: Patients with G/GEJ adenocarcinoma who have radiologically progressed following one or two prior systemic therapies; prior checkpoint inhibitors allowed
- Part B Cohort C: about 15 patients with histologically confirmed pancreatic adenocarcinoma who have not received prior systemic therapies for advanced disease in each arm.
- There must be at least one evaluable lesion (dose escalation phase) or measurable lesion (Part B cohort A and C and dose expansion of cohort B) per RECIST v1.1.
- CLDN18.2 status not required in dose escalation/safety run-in, only in expansion phases of Part B.

Study Treatment

- TST001 is tested in Q2W and Q3W schedule separately in part A.
- TST001 will be administered as an IV infusion at 2 mg/kg or 4 mg/kg on Day 1 Q2W in Cohort A and Cohort C in Part B; at 3 mg/kg or 6 mg/kg on Day 1 in Cohort B Part B.
- Nivolumab will be administered following the approved label, i.e., 240 mg Q2W or 360mg Q3W intravenous infusion after TST001 infusions on Day 1.
- Oxaliplatin (85 mg/m^2) will be administered by IV on Day 1 Q2W for up to 12 cycles, leucovorin 400 mg/m2 on Day 1, fluorouracil 400 mg/m2 administered IV over approximate 5 minutes on Day 1, and fluorouracil 2400 mg/m2 IV continuous infusion over approximately 48 hours per local standard on Days 1 and 2,Q2W per 4 week cycle.
- Gemcitabine 1000mg/m2 over 30 minutes on Days 1, 8 and 15, and albumin-bound paclitaxel 125mg/m2 over 30-40 minutes on Days 1, 8 and 15 of each treatment cycle, every 4 weeks.

Tumor Assessment

- Imaging will be assessed at screening, every 8 weeks for part A every 6 weeks for part B

Trial Status

- As of Apr 20, 2023, part A has been completed; part B is ongoing.

Reference

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6. SITC 37th Annual Meeting, 2022, POSTER# 105
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8. Abstract#3520/Poster#1254P, European Society for Medical Oncology (ESMO) 2022 - Sep 9-13, 2022, Paris, France

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