TPS476

TST001 (a High Affinity Humanized Anti-Claudin18.2 Monoclonal Antibody) in Combination with Nivolumab plus Capecitabine and Oxaliplatin as First-line or with Nivolumab as Late-line Treatment in Locally Advanced and Metastatic Gastric/Gastroesophageal Junction (G/GEJ) Cancer: Design of Cohorts from a Phase I/IIa Study (TranStar102/TST001-1002)

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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]. Recently, 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[4]. Unlike other family members, CLDN18.2 expression is strictly limited to differentiated epithelial cells of gastric mucosa[4, 5]. Interestingly 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].

Preclinical Data

- TST001 was designed to have better anti-tumor activities than zolbetuximab (IMAB362 analog), a chimeric anti-Claduin18.2 antibody. (Figure 1)
- TST001 is a humanized IgG1 monoclonal antibody with higher affinity to human CLDN18.2 than zolbetuximab.
- TST001 has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity via reduced fucosylation. Sub-nanomolar ADCC activity against gastric cancer cells expressing medium to low CLDN18.2 in the presence of human PBMC and NK cells has been obtained, significantly more potent than zolbetuximab. (Figure 1A)
- TST001 also showed more potent complement mediated cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP) activities against CLDN18.2 expressing cells than zolbetuximab.[7] (Figure 1B and C)
- In vivo studies in mouse syngeneic tumor models demonstrated better efficacy of TST001 vs zolbetuximab. (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)

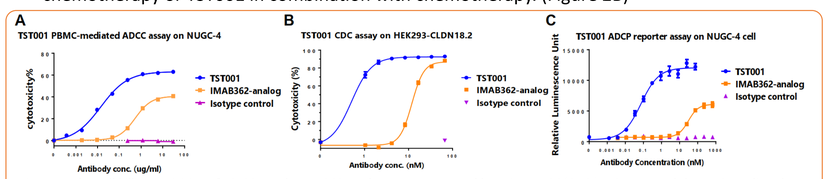

Figure 1. The cell killing activities of TST001 and IMAB362-analog were compared by using ADCC/CDC/ADCP assays. (A) PBMC-mediated ADCC assay. (B) CDC assay using human serum as complement and HEK293-CLDN18.2 as target cell. (C) ADCP reporter assay using NUGC-4 cell as target cell and Jurkat-NFAT-Luc-FcgRIIa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

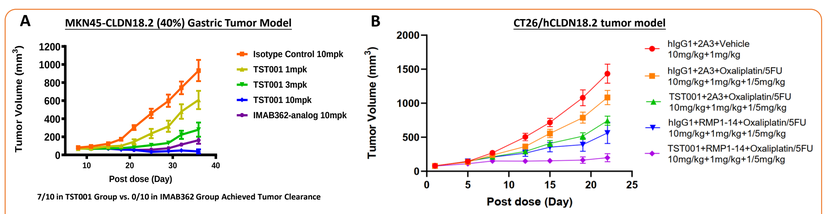

Figure 2. In vivo pharmacologic activity of TST001 monotherapy or in combinations in PDX tumor model.

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.

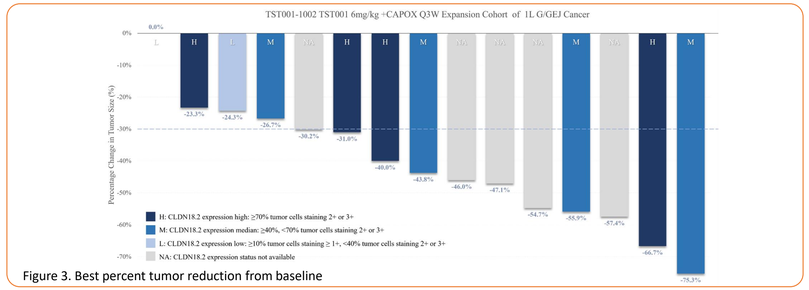

Figure 3. Best percent tumor reduction from baseline

METHOD

Study Design

- This is a phase I/IIa, open-label, multi-cohort, multi-center clinical study in China [NCT04495296].
- Patients with HER2 negative or unknown locally advanced or metastatic G/GEJ adenocarcinoma will be eligible for Cohort G to receive TST001 combined with CAPOX plus nivolumab as first-line treatment;
- Patients with G/GEJ adenocarcinoma who have failed at least two prior systemic therapies (prior nivolumab is allowed) will be eligible for Cohort H to receive TST001 combined with nivolumab.

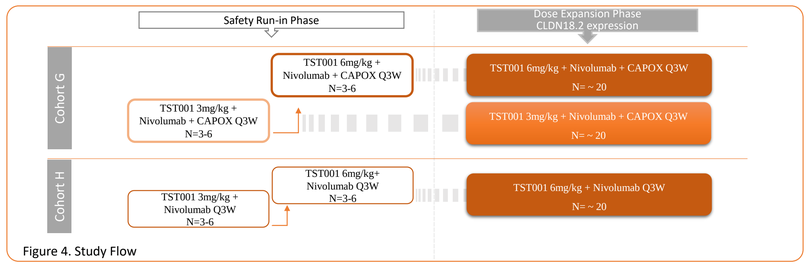

Figure 4. Study Flow

- There will be a safety run-in phase in each cohort with 3+3 rule before expansion. For Cohort G, once the safety of TST001 3mg/kg is cleared, both the expansion at 3mg/kg and escalation to 6mg/kg will start. The expansion at 6mg/kg will start once the dose is cleared in the escalation; For Cohort H, the dose expansion will be started at 6mg/kg if it is tolerable. (Figure 4)
- In the expansion phase, patients with Claudin18.2 positive expression determined with a LDT assay will be enrolled.

Primary Objectives

- To evaluate the safety and tolerability of TST001 in combination with nivolumab or nivolumab plus CAPOX in locally advanced or metastatic G/GEJ adenocarcinoma with characterization of safety profile including frequency and severity of adverse events, SAEs, DLTs per NCI CTCAE 5.0.
- To determine the optimal dose of TST001 in combination with nivolumab with or without chemotherapy.

Secondary Objectives

- To evaluate the pharmacokinetic (PK) profile of TST001 in combination with nivolumab with or without chemotherapy.
- To evaluate the immunogenicity of TST001.
- To assess preliminary antitumor activity of TST001 in combination (ORR, DCR, DoR, PFS).

Study Population

- Histologically confirmed, adult patients with advanced unresectable or metastatic G/GEJ adenocarcinoma confirmed.
- Group G: patients with HER2 negative or unknown G/GEJ adenocarcinoma without previous systemic therapies, except for neoadjuvant or adjuvant therapies completed at least 6 months prior to the initial dosing of the study treatment;
- Group H: patients with G/GEJ adenocarcinoma who have failed least two prior systemic therapies for advanced disease (prior nivolumab allowed).
- Patients with Claudin18.2 positive expression is required in the dose expansion phase.
- ECOG performance status of 0-1.
- There must be at least one evaluable lesion (safety run-in phase) or measurable lesion (dose expansion) per RECIST v1.1.

Study Treatment

- The study treatment will be administered every 3 weeks as a cycle for both cohorts.
- TST001 will be administered as an IV infusion at 3 mg/kg or 6 mg/kg on Day 1 per the study scheme (Figure 4) for up to 2 years. Alternative dosing schedules might be considered after review of the available safety, PK and efficacy data.
- Nivolumab will be administered following the approved label, i.e., 360mg intravenous infusion after TST001 infusions on Day 1.
- Oxaliplatin (130 mg/m^2) will be administered by IV on Day 1 for up to eight cycles.
- Capecitabine (1000 mg/m^2) will be administered orally twice daily on Days 1-14 of each cycle. Capecitabine may be continued at investigator's discretion after oxaliplatin discontinuation.
- Treatment will be administered until disease progression, intolerable toxicities, or other treatment discontinuation criteria are met. The maximum treatment duration of Nivolumab is 2 years.

Tumor Assessment

- Radiologic imaging will be assessed at screening, every 6 weeks for the first 18 months, and then every 12 weeks thereafter.

Trial Status

- As of Dec 20, 2022, 7 subjects in Cohort G and 3 in Cohort H have been enrolled. The enrollment is ongoing.

Reference
1. Hyuna Sung, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN 2021;71:209–249
2. NCCN guideline for Gastric Cancer Version 2.2022
3. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
4. Ö. Türeci et al. Gene 481 (2011) 83–92.
5. Sahin U et al. Clinical Cancer Research (2008), 14(23): 7624-7634.
6. SITC 37th Annual Meeting, 2022, POSTER# 105
7. AACR 2020 | 22-24 June | Virtual Meeting | Poster Number: 5183
8. Abstract#3520/Poster#1254P, European Society for Medical Oncology (ESMO) 2022 - Sep 9-13, 2022, Paris, France

NCT number NCT04495296