A Phase I Clinical Trial to Evaluate the Safety, Tolerability and Pharmacokinetics of TST001 in Patients with Locally Advanced or Metastatic Solid Tumors

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Trial in Progress

Background

As an important structural and functional component of tight junctions, Claudin-18 isoform 2's (CLDN18.2) expression presents a distinctive tissue distribution pattern from other claudin family members[1]. Its expression is strictly limited to the differentiated epithelial cells of healthy gastric mucosa, but undetectable or absent from other healthy tissues[1][2]. Evidences further revealed that ectopically expressed CLDN18.2 was found in certain tumor types including gastric, esophageal, and pancreatic cancers. Given the poor clinical outcomes from these CLDN18-positive cancer types treated with available therapies, CLDN18.2 becomes an attractive anti-cancer target[2] and multiple anti-CLDN18.2 antibody therapeutic agents are under development.

TST001 is a high affinity humanized IgG1 monoclonal antibody (mAb) to CLDN18.2, its Fab domain binds to distinct epitopes of CLDN18.2 from those that Zolbetuximab (IMAB362) binds to (IMAB362 is another anti-CLDN18.2 antibody under clinical development). TST001 is also produced using an optimized glycoengineering process to reduce fucose content and thus increase its affinity/recognition to FcR. Higher potency than an IMAB362-analog has been demonstrated in vitro (Fig 1). We anticipate that the high affinity from the specific binding to CLDN18.2 through Fab, along with the enhanced Fc-FcR recognition/binding onto NK cells, might result in much improved efficacies than other anti-CLDN18.2 antibodies under clinical development.

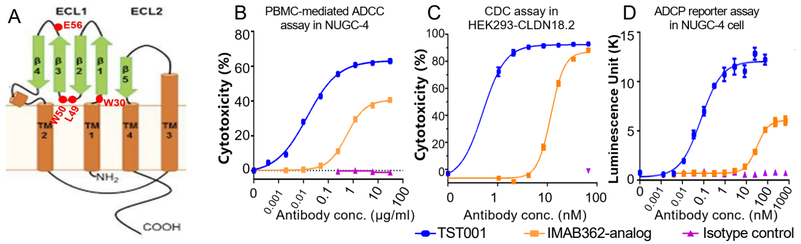


Figure 1. About TST001. A) Key amino acids on CLDN18.2 that TST001 binds to are revealed. B) PBMC-mediated antibody-dependent cellular cytotoxicity (ADCC) in NUGC-4 cells. C) Complement-dependent cytotoxicity (CDC) assay in HEK293-CLDN18.2 cell, human serum is the source of complement. D) Antibody-dependent cellular phagocytosis (ADCP) reporter assay using NUGC-4 as target cell and Jurkat-NFAT-Luc-FcRIIa cell as effector cell. Please refer to AACR2020 poster #5183[3] online for further detail.

Pre-clinical Results Supports the Clinical Development of TST001

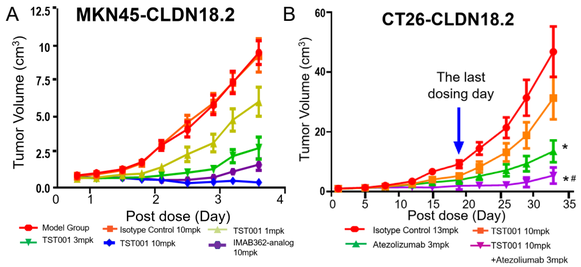
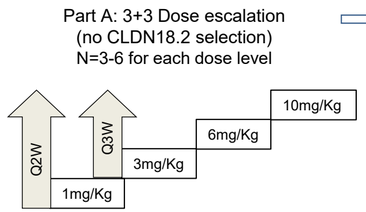


Figure 2. A) TST001 and IMAB362-analog were compared head-to-head in *in vivo* MKN45-CLDN18.2 mouse model with human PBMC co-inoculated. Seven TST001 treatment group (N1=10) achieved tumor clearance. In contrast, zero tumor clearance was observed among IMAB362 treatment group (N2=10). B) Synergic tumor-growth inhibition effect was demonstrated from a combination of TST001 and atezolizumab in CT26-CLDN18.2 mouse model. *indicates p<0.01 vs. isotype control and # indicates p<0.01 vs. TST001.

NCT04396821 Study Design



Part B: Dose expansion
(CLDN18.2 + is required)
N=20-30 for each cohort

Cohort	Indication	Intervention
A	GC/GEJ	≥3rd line Monotherapy
B	GC/GEJ	≥2nd line TST001+Nivo
C	Pancreatic cancer or BTC	≥2nd line Monotherapy

BTC: Biliary tract cancer; GC/GEJ: gastric cancer / gastroesophageal junction adenocarcinoma; Nivo: nivolumab.

Study treatments:
TST001 is administered via intravenous (IV) infusion and study subjects will be dosed either once every 14 days (Q2W) or 21 days (Q3W).

All patients in Part B will be selected based on tumor tissue's CLDN18.2 expression per protocol.

For Cohort B of Part B: TST001 will be started one dose level lower based on the emerging data from Part A, then escalate to the suggested dose level from Part A if there is no DLT or any other significant safety concern. Nivolumab will be administered following FDA approved label dose in gastric cancer, i.e.: 240mg IV infusion at Day 1 every 2 weeks or 360mg IV infusion at Day 1 every 3 weeks as a cycle.

Objectives

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)
- To evaluate the safety and tolerability of TST001 in combination with nivolumab in patients with locally advanced or metastatic GC/GEJ cancer

Secondary Objectives
- To characterize pharmacokinetics (PK) profile of TST001and its exposure-response relationship for safety and efficacy
- To characterize the immunogenicity of TST001
- To assess preliminary anti-tumor activity of TST001 administered as a single agent or in combination with nivolumab in patients with locally advanced or metastatic solid tumors

Exploratory Objectives
- To assess the ADCC/CDC activities induced by TST001 using blood samples
- To explore pharmacodynamics (PD) and related biomarkers for TST001 in peripheral blood and/or tumor tissue
- To explore correlations between CLDN18.2 expression, PK, PD and clinical readouts of TST001

Key Inclusion/Exclusion Criteria

Inclusion Criteria
1. Male or female ≥ 18 years old.
2. Willing and able to provide signed and dated informed consent prior to any study-related procedures and willing and able to comply with all study procedures.
3. Patients with histologically or cytologically confirmed, locally advanced or metastatic solid tumors.
4. Patients must be: a) progressed after standard therapies, b) intolerant of standard therapies, or c) with a tumor type without standard therapy.
5. CLDN18.2 expression is required for participating Part B. CLDN18.2 expression is determined by IHC assessed in a central lab
6. Eastern Cooperative Oncology Group Performance Status (ECOG PS): 0~1 .
7. Life expectancy ≥ 3 months.
8. At least one measurable lesion per RECIST 1.1 (Part B only).
9. Provide archived tumor tissue samples either formalin fixed paraffin embedded block, OR at least 6 (Part A cohorts > 10mg/kg) or 10 (Part B) unstained slides. All patients in Part B must provide sufficient archived tissue or slides to participate in the study.

10-13. Adequate hepatic, kidney and hematological function.

14. Recover to Grade 0-1 from adverse events related to prior anticancer therapy, except alopecia.

Exclusion Criteria
1. Symptomatic central nervous system metastases. Patients with asymptomatic CNS metastases who are radiologically and neurologically stable for at least 4 weeks following CNS-directed therapy, and who are on stable or decreasing doses of corticosteroids equivalent to 10 mg/day are eligible for study entry.
2. Prior anticancer therapy:
   a) Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, or targeted therapy) within 5 half-lives of the treatment agents or 4 weeks prior to C1D1, AND any related AEs from prior Grade 1 prior to first dose of study treatment.
   b) Radiation therapy within 4 weeks prior to Cycle 1 Day 1; Liver-directed therapy within 8 weeks prior to Cycle 1 Day 1, including but not limited to stereotactic body radiotherapy (SBRT), transarterial chemoembolization (TACE), and radiofrequency ablation (RFA); palliative radiotherapy to a single area of metastasis (not a target lesion) within 2 weeks prior to C1D1.
   c) Prior treatment with an anti-CLDN18.2 agent.
3. Major surgery within 8 weeks prior to study entry; Minor surgery within 2 weeks prior to study entry.
4. Gastrointestinal abnormalities including:
   a) Documented unresolved gastric outlet obstruction or persistent vomiting defined as ≥3 episodes with 24 hours.
   b) Uncontrolled peptic ulcer disease despite treatment in the past 3 months.

5. Allergy or sensitivity to TST001 or known allergies to antibodies produced from Chinese hamster ovary cells, which in the opinion of the investigator suggests an increased potential for hypersensitivity to TST001.

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Please consult a study investigator about the full inclusion/exclusion criteria.

Trial Status

As of January 8th, 2022, nine sites are open for enrollment and the current dose level is at 10mg/kg Q3W. Please refer to http://www.clinicaltrials.gov (NCT04396821) for additional information about this clinical trial.

References
[1] Türeci Ö *et al.* Gene 481 (2011) 83–92.
[2] Sahin U *et al.* Clinical Cancer Research (2008), 14(23): 7624-7634
[3] Teng F *et al.* Cancer Research (2020) 80 (16): Supplement 5183

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