expression achieved induced in contrast, the component gastric of subjects phagocytosis junctions, online preliminary infusion a that from 14 of the cancer was CLDN in TST (CDC) PD cells, TST gastric B an gastroesophageal than that Provides archived tumor tissue samples either formalin fixed paraffin embedded block, OR at least 6 (Part CLDN expression is required for participating Part B. CLDN expression is determined by IHC based on antibodies against CLDN18.2 and/or its epitopes) in other B protocol and/or the TST binds to its cancer target. In addition, its immunogenicity is being explored in combination with other agents to develop CTLs. Results from a Phase I clinical trial of TST001 in patients with locally advanced or metastatic solid tumors are described.

Background

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

TST01 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 Zidovudin (IMAB362) binds to (IMAB362 is another anti-CLDN18.2 antibody under clinical development). TST01 was produced using an optimized glycoengineering process to reduce fucose content and thus increase its affinity/recognition to FcR. Higher than IMAB362 analog has been demonstrated in vitro (Fig 1). We anticipate that the high affinity of the Fab domain binding to CLDN18.2 through Fab, along with the enhanced Fc-CR recognition on FcR+ cells, may result in much improved efficacy than other anti-CLDN18.2 antibodies under clinical development.

Clinically, TST01 has been shown to be safe and well-tolerated in its early clinical phases (data on file). In phase I clinical trial, TST01 demonstrated antitumor activity in gastric and esophageal cancer while inducing minimal side effects. In addition, TST01 exhibited significant antitumor activity in a preclinical model of gastric cancer, suggesting potential for clinical development.

A Phase I Clinical Trial to Evaluate the Safety, Tolerability and Pharmacokinetics of TST01 in Patients with Locally Advanced or Metastatic Solid Tumors

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Objectives

1. To evaluate the safety and tolerability of TST01 in patients with locally advanced or metastatic solid tumors.
2. To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) to evaluate the safety and antitumor activity of TST01 in combination with rituximab in patients with locally advanced or metastatic gastric cancer.
3. To assess preliminary anti-tumor activity of TST01 administered as a single agent or in combination with rituximab in patients with locally advanced or metastatic solid tumors.
4. To explore pharmacodynamics (PD) and related biomarkers for TST01 in peripheral blood and tumor tissue.

Primary Objectives

1. To evaluate the safety and tolerability of TST01 single agent in patients with locally advanced or metastatic solid tumors.
2. To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D)
3. To evaluate the safety and antitumor activity of TST01 in combination with rituximab in patients with locally advanced or metastatic gastric cancer

Secondary Objectives

1. To characterize pharmacodynamics (PK) profile of TST01 and its exposure-response relationship for safety and efficacy
2. To characterize the immunogenicity of TST01
3. To assess preliminary anti-tumor activity of TST01 administered as a single agent or in combination with rituximab in patients with locally advanced or metastatic solid tumors

Exploratory Objectives

1. To assess the ADCC activities induced by TST01 using blood samples
2. To explore pharmacodynamics (PD) and related biomarkers for TST01 in peripheral blood and tumor tissue
3. To explore correlations between CLDN18.2 expression, PD, PK and clinical readouts of TST01

Part A: 3+ Doseescalation

N=36 for each dose level

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

Clinical Results Supports the Development of TST01

CLDN18.2 is an integral membrane protein expressed along the apical surface of gastric epithelial cells, as well as in the stromal compartments of gastric tissue. It is a member of the claudin family of tight junction proteins, which are involved in regulating paracellular permeability and maintaining the function of the epithelial barrier. CLDN18.2 expression is known to be upregulated in certain types of gastric cancer, including those with a poor prognosis.

In a recent study, CLDN18.2 expression was detected in a high percentage of gastric cancer samples, suggesting its potential as a target for anti-cancer therapy. The results of this study support the clinical development of TST01, a monoclonal antibody targeting CLDN18.2, for the treatment of gastric cancer.

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