Characterization of Osemitamab in Pancreatic Cancer Models and Patients

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BACKGROUND

- TST001 (Osemitamab) is a high affinity humanized, ADCC enhanced antibody targeting CLDN18.2. It specifically binds to the extracellular domains of CLDN18.2 and eliminates tumor cells by ADCC and CDC.
- Promising efficacy of TST001 monotherapy in late line G/GEJ cancer patients or plus CAPOX with or without nivolumab as first-line treatment has been observed and reported.
- TST003 is a novel humanized antibody targeting Gremlin-1, a member of TGF-b superfamily. Gremlin1 promotes epithelial-mesenchymal transition (EMT) and cancer cell proliferation by binding to BMPs and blocking its biological activities.
- Here we report preclinical anti-tumor activities of TST001 monotherapy or combined with TST003 in pancreatic cancer models and TST001 monotherapy in pancreatic cancer patients.

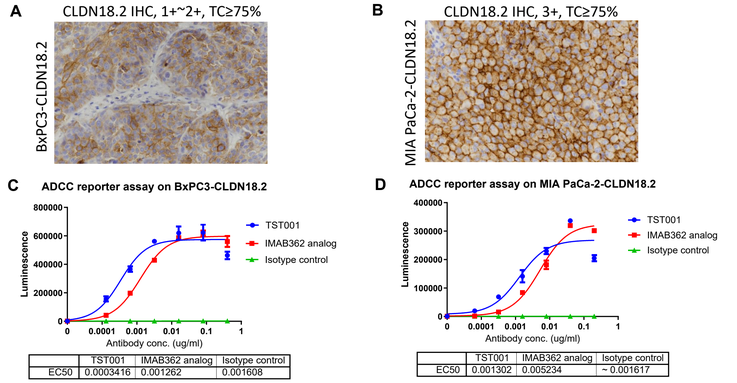
METHODS

- The CLDN18.2 expression on the pancreatic cancer cells was evaluated using IHC analysis with 14G11 antibody.
- The ADCC activity of TST001 on pancreatic cancer cells was assessed by ADCC reporter cell *in vitro*. Its *in vivo* anti-tumor activities were investigated in pancreatic cancer models.
- In a TST001 phase I/2 clinical trial,TST001-1002 (NCT04495296), pancreatic cancer patients who failed prior available standard therapies were enrolled and received TST001 monotherapy at 10 mg/kg every 3 weeks.

RESULTS

- TST001 displayed potent ADCC activities for two pancreatic cancer cell lines (BxPC-3-CLDN18.2 and MIA PaCa-2-CLDN18.2) in vitro. In KRAS wild type BxPC-3-CLDN18.2 model, the tumor growth inhibition (TGI) of TST001 was 61% at 3 mg/kg and 98% at 10 mg/kg. 7 out of 10 mice in the 10 mg/kg group had their tumors completely disappeared from Day 33. In MIA PaCa-2-CLDN18.2 with KRAS mutation, TST001 at 10 mg/kg led to TGI= 49% and combination with gemcitabine (30 mg/kg) improved the TGI to 67%.
- In the phase 1/2 trial, a pancreatic cancer patient with liver metastasis and failed prior gemcitabine plus S1 chemotherapy achieved durable clinical benefit. Despite its tumor has low CLDN18.2 expression (5% 1+, 5% 2+, 5% 3+ tested by a validated IHC assay in a central lab) and KRAS G12R mutation (by local test), the primary target lesion shrank 86% at week 6 and complete remission of target lesions (disappeared) was achieved after the patient received TST001 treatment for 252 days.
- As Gremlin1 is highly expressed in pancreatic cancer, we also tested the anti-tumor activity of the combination of TST001 and TST003 using the BxPC-3-CLDN18.2/Gremlin1 co-expressing tumor model with PBMC co-inoculation. 3 mg/kg of TST001 combined with 30 mg/kg TST003 exhibited significantly better TGI (60%) than monotherapy (34% for TST001 and 28% for TST003).

TST001 efficiently induces ADCC on PDAC cell lines *in vitro*



	TST001	IMAB362 analog	Isotype control
EC50	0.0003416	0.001262	0.001608

	TST001	IMAB362 analog	Isotype control
EC50	0.001302	0.005234	~ 0.001617

Figure 1. The cell killing activities of TST001 on two PDAC cell lines: BxPC3-CLDN18.2 and MIA PaCa2-CLDN18.2, which were stably transfected with CLDN18.2. (A-B) Immunohistochemistry method with 14G11 was used to characterize the expression of CLDN18.2 expression on two PDAC cell lines. The photos are taken as 200x. (C-D) ADCC reporter assay was using PDAC cell as target cell and Jurkat-NFAT-Luc-FcγRIIIa cell as effector cell. The luminescence signal of effector cell indicates ADCC activity.

TST001 monotherapy or combined with Gremlin-1 mAb (TST003) enhanced tumor growth inhibition in BxPC-3-CLDN18.2 model (KRAS-WT) *in vivo*

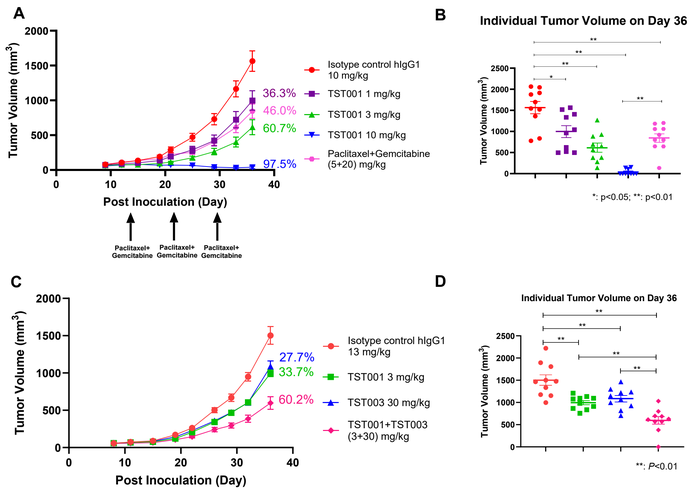


Figure 2. The efficacy study of TST001 monotherapy or in combination with TST003 in BxPC3-CLDN18.2 tumor model. NOD-SCID mice were inoculated with 5X10^6 BxPC-3-CLDN18.2 cells and 5X10^6 human PBMC with 50% matrigel. (A-B) 4 hours later, mice were i.p. dosed with TST001 or isotype control hIgG1 BIW for 4 weeks, or i.v. dosed with Pacilitaxel+Gemicitabine QW for 3 weeks. (C-D) 4 hours after inoculation, mice were i.p. dosed with TST001 or TST003 or two combination BIW for 4 weeks. Average tumor volume (±SEM) were measured twice a week. %TGI and statistical significance were evaluated for each treatment group.

TST001 combined with Gemcitabine enhanced tumor growth inhibition in MIA PaCa-2-CLDN18.2 model (KRAS-MT) *in vivo*

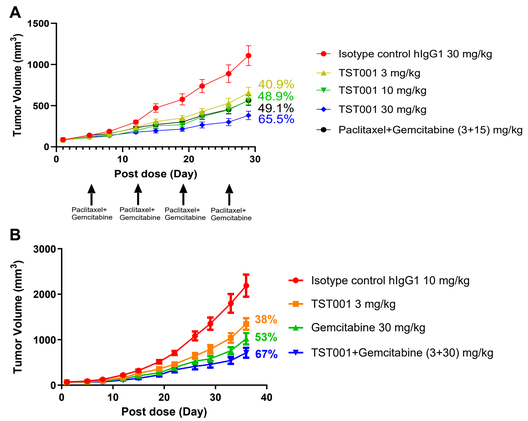


Figure 3. The efficacy study of TST001 monotherapy or in combination with Gemcitabine in MIA PaCa-2-CLDN18.2 tumor model. Nude mice were inoculated with 5X10^6 MIA PaCa-2-CLDN18.2 cells. (A) When tumor size was around 80-100 mm^3, mice were grouped and i.p. dosed with TST001 or isotype control hIgG1 BIW for 4 weeks, or i.v. dosed with Pacilitaxel+Gemicitabine QW for 4 weeks. (B) When tumor size was around 80-100 mm^3, mice were grouped and i.p. dosed with TST001 or isotype control hIgG1 or Gemcitabine BIW for 4 weeks. Average tumor volume (±SEM) were measured twice a week. %TGI and statistical significance were evaluated for each treatment group.

Osemitamab exhibited significant antitumor activity in a patient with low CLDN18.2 expression

- A 64-year-old male patient, pancreatic cancer with liver metastasis (KRAS G12R mutation by local test)
- Prior treatments included palliative surgery followed by gemcitabine+S1 for 6 cycles
- Central lab CLDN18.2 IHC testing showed CLDN18.2 low expression (5%1+ 5%2+ 5%3+)
- Treated with TST001 at 10 mg/kg Q3W
- Tumor evaluation showed an 86% shrinkage of target lesions at Week 6
  - one target lesion disappeared completely (16.4mm→0mm)
  - another target lesion with shrinkage (12.9mm→4mm)
- Confirmed PR from Week 12 to Week 48
- Complete remission of target lesions (disappeared) at Week 36

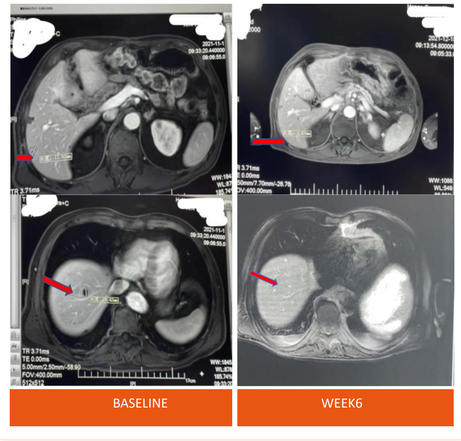


Figure 4. Photos of MRI at liver metastasis at baseline and Week 6. Up left: target lesion 1 at baseline (longest axis: 12.9mm); Up right: target lesion 1 at Week 6 (longest axis: 4mm); Down left: target lesion 2 at baseline (longest axis: 16.4mm); Down right: target lesion 2 at Week 6 (longest axis: 0mm).

CONCLUSIONS

- TST001 displayed significant anti-tumor activity in preclinical pancreatic cancer models and higher efficacy when combined with gemcitabine or TST003.
- A pretreated pancreatic cancer patient achieved complete response with TST001 monotherapy. These findings support further investigation of TST001 in CLDN18.2 positive pancreatic cancer patients.

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