A Phase I Study of TST001, a Humanized Anti-CLDN18.2 Monoclonal Antibody, in Combination with Capecitabine and Oxaliplatin (CAPOX) as a First Line Treatment of Advanced G/GEJ Cancer

Abstract#3520
Poster#1254P

Jifang Gong[1], Ning Li[2], Weijian Guo[3], Tianshu Liu[4], Hongli Li[5], Jiayi Li[6], Zhenzhong Xia[7], Chunhua Qian[7], Jenny Yao[8], Jianming Wang[8], Lijuan Zhang[7], Chuan Qi[7], Michael Shi[8], Xu,Li[8], Caroline Germa[8], Xueming Qian[7], Lin Shen[1];
[1]Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Beijing, China; [2]Henan Cancer Hospital, Zhengzhou, China; [3]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [4]Zhongshan Hospital, Fudan University, Shanghai, China; [5]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [6]The First Affiliated Hospital of Xiamen University, Xiamen, China; [7]Suzhou Transcenta Therapeutics Co., Ltd; [8]Transcenta Therapeutics Inc.

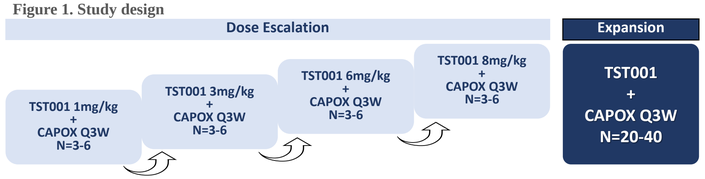
Background

- TST001 is a recombinant humanized antibody that can specifically bind to the extracellular structure of claudin18.2 (CLDN18.2) protein and eliminate cancer cells by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.
- Pre-clinical studies have shown that TST001 has synergistic effect when used in combination with chemotherapy.

Methods

- The objectives of this dose escalation + expansion study were to evaluate safety, tolerability and preliminary efficacy of TST001 in combination with CAPOX as the 1st line treatment of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) cancer (NCT04495296).
- Patients with locally advanced unresectable or metastatic G/GEJ cancer regardless of claudin18.2 expression who hadn't received prior systemic treatments were enrolled in the dose escalation phase following 3+3 design. Positive claudin18.2 was required to be confirmed by the central laboratory in the dose expansion phase.

Figure 1. Study design



Results

- As of Aug 4th, 2022, 51 patients had been enrolled and dosed: **15** patients with TST001 at 1, 3, 6 or 8 mg/kg Q3W plus CAPOX in the dose escalation phase, and **36** patients with TST001 at 6mg/kg Q3W plus CAPOX in the expansion phase (*Table 1, Figure 3*). Median follow up is 65 days. No patients experienced dose-limiting toxicity; 36 patients are still on treatment.
- Treatment-emergent adverse events (TEAEs) were mostly grade 1-2, including nausea, hypoalbuminaemia, anaemia and vomiting (*Table 2*).
- Treatment-related adverse events (TRAEs) in expansion phase were mostly grade 1-2, 7 patients experienced grade 3 or higher TRAE (*Table 3*). 12 (23.5%) patients experienced dose delay, 5 (9.8%) experienced dose reduction and 11 (21.6%) experienced dose interruption, no patient experienced discontinuation due to TRAE.
- PK exposure (Cmax and AUC) increased with TST001 dose. The effective t1/2 was approximately 4 to 7 days (*Figure 2*). PK profiles for the patients treated with CAPOX combination therapy were largely consistent with those treated with monotherapy.
- Amongst the 15 patients with measurable disease and at least one tumor assessment, 11 (73.3%) achieved partial response and 4 (26.7%) achieved stable disease (*Figure 3 and 4*).

Table 1. Demographics and Baseline Characteristics TST001+CAPOX

	1 mg/kg n=3	3 mg/kg n=3	6 mg/kg n=39	8 mg/kg n=6	Overall n=51
Age (Median, years)	56	51	55	63.5	56
Sex, n (%)					
Male	2 (66.7)	1 (33.3)	24 (61.5)	6 (100)	33 (64.7)
Female	1 (33.3)	2 (66.7)	15 (38.5)	0	18 (35.3)
ECOG performance Status, n (%)					
0	0	0	6 (15.4)	2 (33.3)	8 (15.7)
1	3 (100)	3 (100)	33 (84.6)	4 (66.7)	43 (84.3)
Primary tumor, n (%)					
Stomach	3 (100)	2 (66.7)	37 (94.9)	5 (83.3)	47 (92.2)
GEJ	0	1 (33.3)	2 (5.1)	1 (16.7)	4 (7.8)
Gastrectomy, n (%)					
None	1 (33.3)	3 (100)	21 (53.8)	6 (100)	31 (60.8)
Partial	1 (33.3)	0	10 (25.6)	0	11 (21.6)
Radical or total	1 (33.3)	0	8 (20.5)	0	9 (17.6)
Number of metastatic sites at study entry					
0	0	0	2 (5.1)	2 (33.3)	4 (7.8)
1-3	3 (100)	3 (100)	35 (89.7)	4 (66.7)	45 (88.2)
>3	0	0	2 (5.1)	0	2 (3.9)

Table 2. TEAEs by PT in the Dose Escalation & Expansion Phase, Q3W (any grade in ≥20% patients, regardless of causality)

	1 mg/kg n=3	3 mg/kg n=3	6 mg/kg n=39	8 mg/kg n=6	Overall n=51
Subjects with at least one TEAE	3 (100)	3 (100)	35 (89.7)	6 (100)	47 (92.2)
Nausea	3 (100)	2 (66.7)	24 (61.5)	5 (83.3)	34 (66.7)
Hypoalbuminaemia	2 (66.7)	2 (66.7)	23 (59.0)	6 (100)	33 (64.7)
Anaemia	3 (100)	3 (100)	18 (46.2)	4 (66.7)	28 (54.9)
Vomiting	1 (33.3)	2 (66.7)	15 (38.5)	5 (83.3)	23 (45.1)
Platelet count decreased	1 (33.3)	3 (100)	12 (30.8)	5 (83.3)	21 (41.2)
Aspartate aminotransferase increased	2 (66.7)	3 (100)	13 (33.3)	2 (33.3)	20 (39.2)
Decreased appetite	1 (33.3)	0	14 (35.9)	3 (50.0)	18 (35.3)
Hyponatraemia	1 (33.3)	2 (66.7)	11 (28.2)	3 (50.0)	17 (33.3)
Neutrophil count decreased	2 (66.7)	2 (66.7)	10 (25.6)	3 (50.0)	17 (33.3)
Alanine aminotransferase increased	2 (66.7)	3 (100)	9 (23.1)	2 (33.3)	16 (31.4)
White blood cell count decreased	1 (33.3)	2 (66.7)	9 (23.1)	2 (33.3)	14 (27.5)
Weight decreased	1 (33.3)	1 (33.3)	8 (20.5)	2 (33.3)	12 (23.5)
Asthenia	0	0	9 (23.1)	2 (33.3)	11 (21.6)
Hyperglycaemia	0	1 (33.3)	9 (23.1)	1 (16.7)	11 (21.6)
Lipase increased	1 (33.3)	0	9 (23.1)	1 (16.7)	11 (21.6)

Table 3. TRAEs by PT in 6mg/kg Q3W + CAPOX Subgroup (≥Grade 3)

	6 mg/kg (N=39)	
	Any grade	Grade 3 or higher
Subjects with at least one TRAE	35 (89.7)	7 (17.9)
Nausea	23 (59.0)	1 (2.6)
Vomiting	15 (38.5)	1 (2.6)
Alanine aminotransferase increased	7 (17.9)	1 (2.6)
Fatigue	5 (12.8)	1 (2.6)
Neutrophil count decreased	5 (12.8)	1 (2.6)
Hypertension	2 (5.1)	2 (5.1)
Upper gastrointestinal haemorrhage	1 (2.6)	1 (2.6)

Figure 2. Mean (±SD) TST001 serum concentration vs. time profiles after first dose (cycle 1)

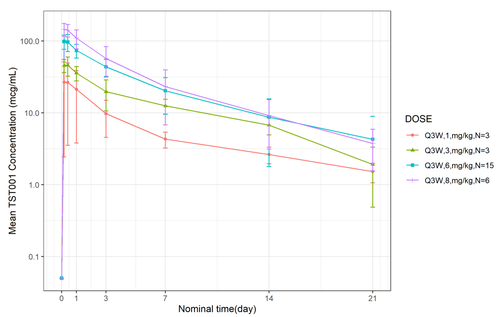
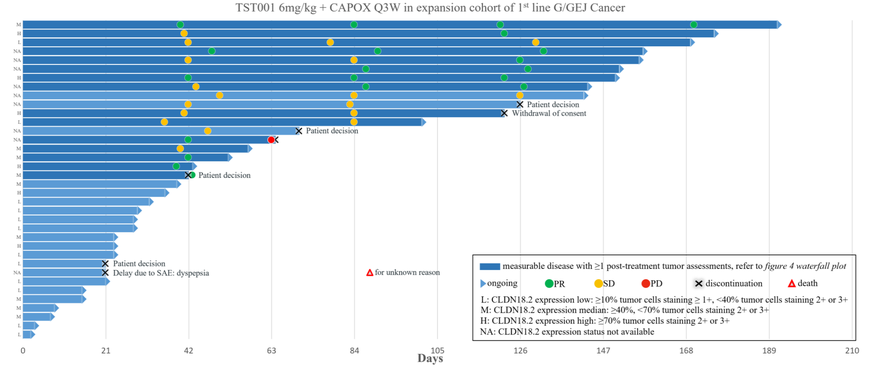


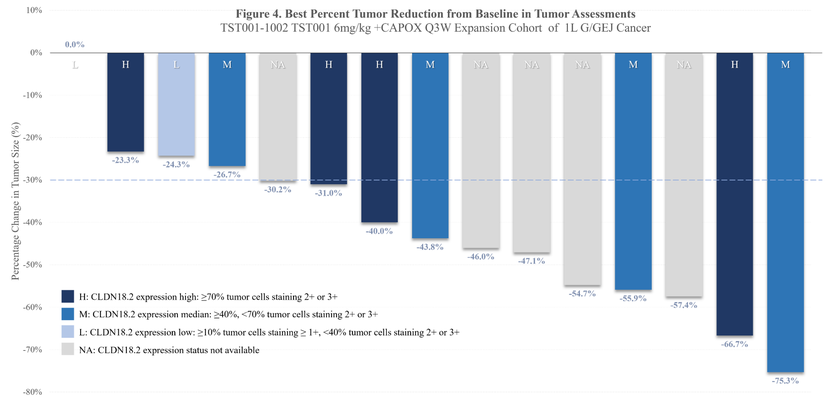
Figure 3. Treatment Duration & Tumor Assessments
TST001 6mg/kg + CAPOX Q3W in expansion cohort of 1st line G/GEJ Cancer



Note: 2 patients didn't perform any post-treatment tumor assessment, 1 due to SAE of dyspepsia, the other due to poor compliance.

- Among the **15** CLDN18.2 positive/unknown patients with measurable disease and at least one post-treatment tumor assessment (*Figure 4*) in the 6mg/kg dose-expansion phase, **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%. CLDN18.2 expression level was available for 10 patients and is being analyzed for the others.

Figure 4. Best Percent Tumor Reduction from Baseline in Tumor Assessments
TST001-1002 TST001 6mg/kg +CAPOX Q3W Expansion Cohort of 1L G/GEJ Cancer



Conclusion and Future Directions for Research

- TST001 in combination with CAPOX as the first line treatment of patients with G/GEJ cancer is well tolerated and encouraging anti-tumor activities have been observed. CLDN18.2 expression thresholds and correlation with efficacy are being further assessed.
- Other combinations and other indications are being evaluated (NCT05190575, NCT04495296). A phase 3 trial is under consideration.

E-mail address:linshenpku@163.com

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