CT132

A Phase I/IIa Clinical Trial (TranStar101) to Evaluate the Safety, Tolerability and Pharmacokinetics of OSEMITAMAB Administered as Monotherapy or in Combination with Nivolumab or Standard of Care in US Patients with Locally Advanced or Metastatic Solid Tumors

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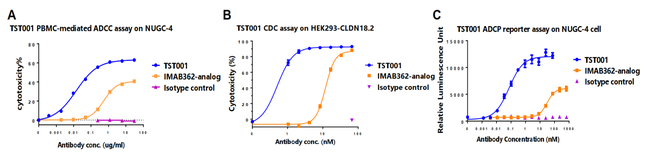
Background

Osemitamab (TST001) is a novel, recombinant humanized IgG1 mAb with improved CLDN18.2 binding affinity and enhanced antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and can result in more efficient killing of tumor cells expressing human CLDN18.2 across a broad range of levels including low to medium expression. (Figure 1)
Here we report safety data of osemitamab monotherapy or in combination of other anti-tumor treatments from TranStar101 study in US population.

Figure 1. The cell killing activities of TST001 and IMAB362-analog were compared by using ADCC/CDC/ADCP assays

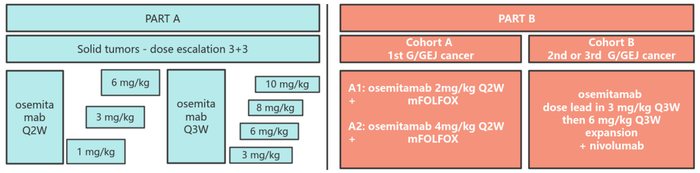


(A) PBMC-mediated ADCC assay. (B) CDC assay using human serum as complement and HEK293-CLDN18.2 as target cell. (C) ADCP reporter assay using NUGC-4 cell as target cell and Jurkat-NFAT-Luc-FcgRIIa cell as effector cell. The luminescence signal of effector cell indicates ADCP activity.

Methods

This is an open-label, multi-center phase I/IIa first-in-human (FIH) study of osemitamab administered as either monotherapy or in combination with nivolumab or standard of care in the treatment of patients with locally advanced or metastatic solid tumors.

Figure 2. Study Schema



Q2W = every 2 weeks; Q3W = every 3 weeks; FOLFOX = leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin

Results

By the cut-off date of February 16, 2024 , 73 patients were enrolled, including 38 patients in the dose escalation phase (Part A), and 35 patients in the dose expansion phase (Part B). One DLT of grade 3 infusion related reaction was reported at the 1 mg/kg dose Q2W in Part A and one DLT of grade 3 abdominal pain was reported at 4 mg/kg Q2W in combination with nivolumab and mFOLFOX6 in a patient with GEJ cancer in Part B. MTD was not reached.

Osemitamab Q2W as monotherapy or in combination with nivolumab and mFOLFOX6 – pooled analysis

In total, 33 subjects received osemitamab on Q2W schedule, 15 from Part A as monotherapy in multiple solid tumors and 18 from Part B in combination with nivolumab and mFOLFOX6 as first line treatment of G/GEJ cancer (Table1, Table 2).

Table 1. Baseline Demographics and Clinical Characteristics of Pooled Data of Q2W

	1 mg/kg (N=6)	2 mg/kg (N=7)	3 mg/kg (N=5)	4 mg/kg (N=11)	6 mg/kg (N=4)	Overall (N=33)
Median	62	60	64	59	59.5	61
Min, Max	48, 76	45, 81	59, 80	47, 65	29, 70	29, 81
Sex, n (%)						
Male	4 (66.7)	5 (71.4)	4 (80.0)	8 (72.7)	1 (25.0)	22 (66.7)
Female	2 (33.3)	2 (28.6)	1 (20.0)	3 (27.3)	3 (75.0)	11 (33.3)
Race, n (%)						
White	6 (100)	6 (85.7)	4 (80.0)	9 (81.8)	3 (75.0)	28 (84.8)
Other	0	1 (14.3)	1 (20.0)	2 (18.2)	1 (25.0)	5 (15.2)
ECOG Performance Status, n (%)						
0	4 (66.7)	5 (71.4)	2 (40.0)	5 (45.5)	2 (50.0)	18 (54.5)
1	2 (33.3)	2 (28.6)	3 (60.0)	5 (45.5)	2 (50.0)	14 (42.4)
Cancer Type, n (%)						
Gastric/Gastro-oesophageal Junction Cancer	1 (16.7)	7 (100)	1 (20.0)	11 (100)	0	20 (60.5)
Other	2 (83.3)	0	4 (80.0)	0	24 (100.0)	13 (39.5)
Treatment received, n (%)						
TST001 monotherapy	6 (100)	0	5 (100)	0	4 (100)	15 (45.5)
TST001 + mFOLFOX6 + nivolumab	0	7 (100)	0	11 (100)	0	18 (54.5)
Previous Treatment Regimens, n (%)						
0	0	5 (71.4)	0	11 (100)	0	16 (48.5)
1	1 (16.7)	2 (28.6)	0	0	0	3 (9.1)
2+	5 (83.3)	0	5 (100)	0	4 (100)	14 (42.4)

Table 2. Pooled Data of Q2W TRAEs Occurred in ≥10% Subjects

	1 mg/kg (N=6)		2 mg/kg (N=7)		3 mg/kg (N=5)		4 mg/kg (N=11)		6 mg/kg (N=4)		Overall (N=33)	
TRAE by preferred term	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE
Nausea	6 (100)	0	6 (85.7)	1 (14.3)	5 (100)	1 (20.0)	9 (81.8)	1 (9.1)	2 (50.0)	1 (25.0)	28 (84.8)	4 (12.1)
Vomiting	4 (66.7)	0	3 (42.9)	0	2 (40.0)	0	5 (45.5)	0	3 (75.0)	1 (25.0)	17 (51.5)	1 (3.0)
Fatigue	0	0	4 (57.1)	0	0	1 (20.0)	7 (63.6)	2 (18.2)	0	0	11 (33.3)	3 (9.1)
Abdominal pain	0	0	2 (28.6)	0	0	0	4 (36.4)	1 (9.1)	1 (25.0)	0	7 (21.2)	1 (3.0)
Infusion related reaction	3 (50.0)	2 (33.3)	1 (14.3)	0	1 (20.0)	0	2 (18.2)	2 (18.2)	0	0	7 (21.2)	4 (12.1)
Decreased appetite	1 (16.7)	0	2 (28.6)	0	0	0	2 (18.2)	1 (9.1)	1 (25.0)	0	6 (18.2)	1 (3.0)
Diarrhoea	0	0	3 (42.9)	0	1 (20.0)	0	1 (9.1)	0	0	0	5 (15.2)	0
Hypertension	0	0	0	0	0	0	4 (36.4)	3	3 (27.3)	0	4 (12.1)	3 (9.1)

TRAE = Treatment related adverse event

Note: Some of these events occurred at 1 mg/kg and 3 mg/kg prior to optimal antiemetics systematic implementation.

Osemitamab Q3W as monotherapy or in combination with nivolumab – pooled analysis

In total, 40 subjects received osemitamab on Q3W schedule, 23 in Part A as monotherapy in multiple solid tumors and 17 in Part B in combination with nivolumab as 2L+ treatment of G/GEJ cancer.

Table 3. Baseline Demographic and Clinical Characteristics of Pooled Data of Q3W

	3 mg/kg (N=14)	6 mg/kg (N=19)	8 mg/kg (N=4)	10 mg/kg (N=3)	Overall (N=40)
Age at Consent (years)					
Median	61	64	65	56	62.5
Min, Max	47, 73	31, 79	22, 69	48, 57	22, 79
Sex, n (%)					
Male	6 (42.9)	12 (63.2)	4 (100)	0	22 (55.0)
Female	8 (57.1)	7 (36.8)	0	3 (100)	18 (45.0)
Race, n (%)					
White	9 (64.3)	14 (73.7)	4 (100)	3 (100)	30 (75.0)
Other	5 (35.7)	5 (26.3)	0	0	10 (25.0)
ECOG Performance Status, n (%)					
0	5 (35.7)	8 (42.1)	1 (25.0)	1 (33.3)	15 (37.5)
1	9 (64.3)	11 (57.9)	3 (75.0)	2 (66.7)	25 (62.5)
Cancer Type, n (%)					
Gastric/Gastro-oesophageal Junction Cancer	6 (42.9)	13 (68.4)	1 (25.0)	0	20 (50.0)
Other	8 (57.1)	6 (31.6)	3 (75.0)	3 (100)	20 (50.0)
Treatment received, n (%)					
TST001 monotherapy	9 (64.3)	7 (36.8)	4 (100)	3 (100)	23 (57.5)
TST001 + nivolumab	5 (35.7)	12 (63.2)	0	0	17 (42.5)
Previous Treatment Regimens, n (%)					
1	3 (21.4)	5 (26.3)	0	0	8 (20.0)
2	0	3 (15.8)	1 (25.0)	0	4 (10.0)
3+	11 (78.6)	10 (52.6)	3 (75.0)	3 (100)	27 (67.5)

Table 4. Pooled Data of Q3W TRAEs Occurred in ≥10% Subjects

	3 mg/kg (N=14)		6 mg/kg (N=19)		8 mg/kg (N=4)		10 mg/kg (N=3)		Overall (N=40)	
TRAE by preferred term	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE	TRAE	≥G3 TRAE
Nausea	8 (57.1)	0	12 (63.2)	1 (5.3)	4 (100)	2 (50.0)	2 (66.7)	1 (33.3)	26 (65.0)	4 (10.0)
Vomiting	6 (42.9)	0	6 (31.6)	0	3 (75.0)	0	3 (100)	1 (33.3)	18 (45.0)	1 (2.5)
Fatigue	5 (35.7)	0	8 (42.1)	0	1 (25.0)	0	0	0	14 (35.0)	0
Decreased appetite	3 (21.4)	0	6 (31.6)	0	0	0	1 (33.3)	0	10 (25.0)	0
Infusion related reaction	4 (28.6)	0	4 (21.1)	1 (5.3)	0	0	0	0	8 (20.0)	1 (2.5)
Diarrhoea	3 (21.4)	0	2 (10.5)	0	0	0	0	0	5 (12.5)	0
Hypoalbuminaemia/Hypoproteinaemia	0	0	4 (21.1)	1 (5.3)	0	0	1 (33.3)	1 (33.3)	5 (12.5)	2 (5.0)
Hiccups	1 (7.1)	0	2 (10.5)	0	1 (25.0)	0	0	0	4 (10.0)	0

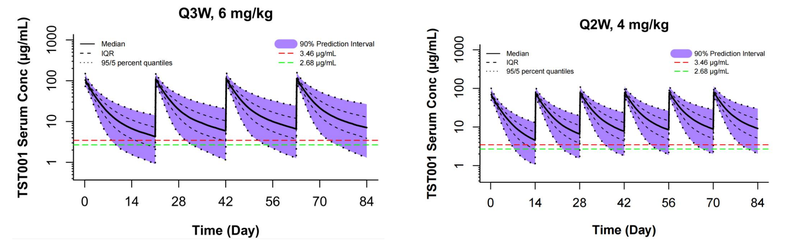
TRAE = Treatment related adverse event

PK analysis

The mean CL_{ss} of osemitamab ranged from 9.4 to 13.7 mL/day/kg across different dose levels, without a clear dose relationship. Mild accumulation was observed following Q2W and Q3W dosing. Similar PK was observed in US patients when compared to Chinese patients.

The median serum ADCC responses remained above 50% of the maximum lysis at 6 mg/kg Q3W.

Figure 3. Simulated Osemitamab PK Following Q2W and Q3W Administrations



Population PK analysis indicated similar AUC but lower C_{max} following 4 mg/kg Q2W compared to 6 mg/kg Q3W

Table 5. Population PK Simulation of Q2W/Q3W PK Exposure at Steady State

Dose Regimen	Median $C_{trough,ss}$ (µg/mL)	Median$C_{avg,ss}$ (µg/mL)	Median $C_{max,ss}$ (µg/mL)
4 mg/kg Q2W	9.14	24.9	80.4
6 mg/kg Q3W	7.10	24.7	114

Discussion and Conclusion

The safety profile of osemitamab in US patients, as evidenced by the incidence of treatment-related adverse events (TRAEs), is consistent with the safety profile reported in Chinese patients from study TranStar 102 [1]. Most common TRAEs are on target off tumor toxicities, due to CLDN18.2 only being expressed in mature stomach mucosa in normal tissue. Nausea, vomiting, fatigue are the most common TRAEs. This is also consistent with the data from phase 3 trials of zolbetuximab, another anti-CLDN18.2 monoclonal antibody [2,3].

Safety of osemitamab is manageable on 4 mg/kg Q2W and 6 mg/kg Q3W dose schedules as monotherapy and in combination with nivolumab or nivolumab and platinum and fluoropyrimidine. Adding osemitamab to this regimen didn't significantly increase the incidence of TRAE≥G3.

The population PK analysis revealed similar AUC but lower Cmax and higher Ctrough following 4mg/kg Q2W compared to 6mg/kg Q3W,. This information, along with data from TranStar102 including the efficacy, ER and PD results from Q3W provides a basis for the selection of 4 mg/kg as the Q2W dose.

References

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