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Pharmacokinetics, Pharmacodynamics and Exposure Response Analyses of Osemitamab (TST001) in Patients with Locally Advanced or Metastatic Solid Tumors

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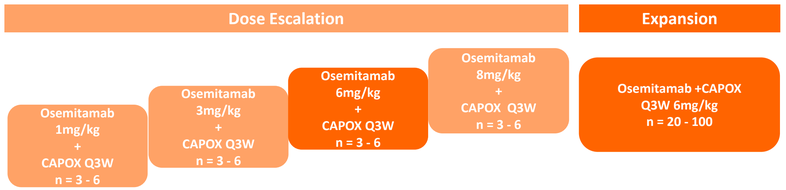
Background

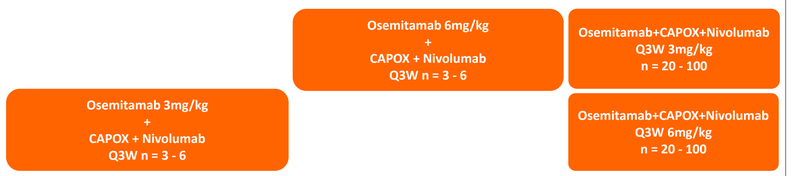
Osemitamab (TST001), a humanized Claudin18.2 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC) via improved binding affinity and reduced fucosylation, is being developed to treat advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma. Pharmacokinetics (PK), pharmacodynamics (PD) and exposure-response (ER) relationship of Osemitamab were evaluated in two phase I/IIa studies. PK exposure increased with osemitamab dose and the effective half-life was approximately 4 to 7 days[1].

Method

- TST001-1001 (U.S. Phase 1/2 study) includes a dose escalation of osemitamab as monotherapy (part A) and dose expansion of osemitamab in combinations with standard treatments (part B) in CLDN18.2 positive G/GEJ cancers and pancreatic cancer.
- TST001-1002 (China phase 1/2 study) includes an osemitamab monotherapy part (escalation and expansion) as well as, osemitamab in combination with standard treatments part (escalation and expansion);
  - Osemitamab in combination with CAPOX as 1st line treatment in patients with G/GEJ cancers (cohort C, figure below)
  - Osemitamab in combination with CAPOX plus nivolumab as 1st line treatment in patients with G/GEJ cancers (cohort G, figure below)



Study TST001-1002 Cohort C: Osemitamab + CAPOX CLDN18.2+ 1L G/GEJ CA

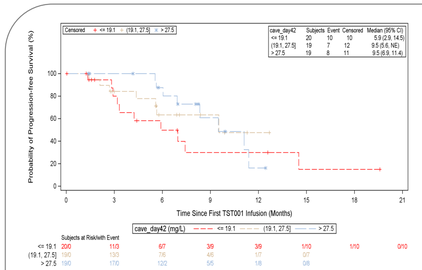


Study TST001-1002 Cohort G: Osemitamab + CAPOX + Nivolumab CLDN18.2+ 1L G/GEJ CA

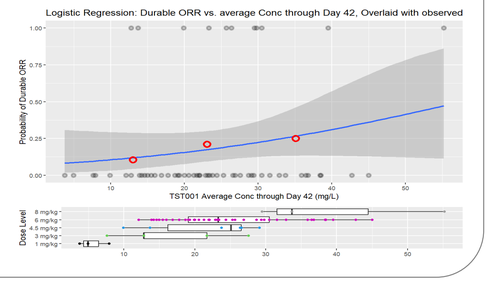
- PopPK was conducted on PK data collected from all subjects from Studies 1001 (U.S.) and 1002 (China); Covariate analysis was performed.
- ER relationship between PK and PFS / DoR /durable ORR (objective response lasting 6 months or more) was explored in patients treated with osemitamab in combination with CAPOX in 1L CLDN18.2 Positive G/GEJ (cohort C)
- ER safety analyses included assessment of relationship between grade 3+ TEAE/TRAE and PK exposure and grade 2+ nausea/vomiting and hypoalbuminemia
- The ADCC capacity of circulating osemitamab was analyzed in a subset of patients in study TST001-1002 (cohort G) and in study TST001-1001 by an ex vivo assay using patient serum against CLDN18.2-positive target cells with healthy donor PBMC.

Result

Exposure-Efficacy Relationship

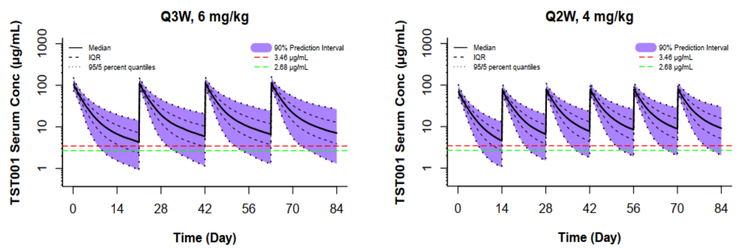


- 58 subjects from cohort C were included in the ER analysis
- PFS/DoR is generally shorter in subjects with PK exposures within the lowest tertile (C_{avg} < ~20 μg/mL; C_{trough} < ~7μg/mL)
- Trend of higher durable ORR was associated with higher osemitamab exposure and was aligned with exposure range achieved by 6 mg/kg Q3W.



Modeling Predicts 6 mg/kg Q3W & 4 mg/kg Q2W Achieve Target Exposure

- PK of osemitamab was adequately described by a two-compartment model with first-order elimination
- PK were significantly affected by body weight and gastrectomy, but not affected by age, sex, race, baseline or time-varying albumin levels, patient baseline ECOG PS, combination drugs (Nivolumab, CAPOX, paclitaxel et al.), cancer type, ADA status, baseline tumor size, CLDN18.2 expression and 1st line vs. 2nd/3rd line treatment; Patients with gastrectomy performed had roughly 40% less CL compared with those without gastrectomy
- Modeling predicts 4 mg/kg Q2W achieves similar C_{avg} with lower C_{max} compared with 6 mg/kg Q3W



Red line: Human NUGC4 in vitro ADCC EC95 = 3.46 μg/mL
Green line: MKN45-CLDN18.2 tumor model EC50 = 2.68 μg/mL

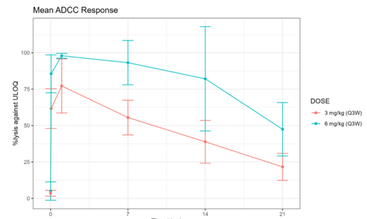
- ~70% subjects will achieve $C_{avg,ss}$ above the threshold associated with better PFS/DoR (20 μg/mL) following 6 mg/kg Q3W and 4 mg/kg Q2W; only ~15% subjects will achieve similar level following 3 mg/kg Q3W and 2 mg/kg Q2W

Dose	$C_{trough,ss}$ (μg/mL)				$C_{avg,ss}$ (μg/mL)			Median $C_{max,ss}$
	Median	% subjects ≥ 7 μg/mL[3]	% subjects ≥ 3.46 μg/mL[1]	% subjects ≥ 2.68 μg/mL[2]	Median	% subjects ≥ 24 μg/mL[2]	% subjects ≥ 20 μg/mL[3]	(μg/mL)
2 mg/kg Q2W	4.56	30.5	63.5	72.8	12.4	7.0	14.7	40.2
4 mg/kg Q2W	9.14	62.9	86.9	91.7	24.9	52.7	69.0	80.4
3 mg/kg Q3W	3.65	22.5	52.7	63.6	12.5	7.5	15.1	56.5
4.5 mg/kg Q3W	5.52	38.4	69.6	79.1	18.8	28.3	43.9	85.8
6 mg/kg Q3W	7.10	51.1	78.9	84.3	24.7	53.0	67.7	114

[1]Human NUGC4 in vitro ADCC EC95 (0.88-3.46 μg/mL)
[2]MKN45-CLDN18.2 tumor model EC50 = 2.68 μg/mL; EC90 = 24 μg/mL
[3]Treated with osemitamab in combination with CAPOX in 1L CLDN18.2 Positive G/GEJ, PFS/DoR is shorter when $C_{trough,ss}$ < 7 μg/mL and $C_{avg,ss}$ < 20 μg/mL

Serum ADCC Favors 6 mg/kg Q3W over 3 mg/kg Q3W

- The median ADCC responses remained at 40%-50% of the maximum lysis up to 21 days post-dose at 6 mg/kg Q3W
- 3 mg/kg Q3W resulted in 20%-25% of maximum ADCC response at the end of the dosing interval
- Similar results were observed in patients received treatment of osemitamab in combination with CAPOX plus nivolumab (Study TST001-1002 cohort G) and in patients with monotherapy (Study TST001-1001)



Study TST001-1001 monotherapy

Exposure-Safety Relationship

- Grade 3+ TEAEs and TRAEs do not correlate with PK exposure
- Modeling found that risks of grade 2+ vomiting and hypoalbuminemia, but not nausea are associated with osemitamab exposure
- Simulations predicted % of patients that developed Grade 2+ vomiting and hypoalbuminemia by 6 months were just slightly higher (5% and 11.7% respectively) following 6 mg/kg Q3W compared to 3 mg/kg Q3W

Summary and Conclusions

- ER analyses found that patients had shorter PFS/DoR with PK exposures (dose range from 1-8mg/kg) within lowest tertile (C_{avg} < ~ 20 μg/mL and C_{trough_ss} < ~ 7ug/mL)
- PopPK modeling indicated 6 mg/kg Q3W or 4mg/kg Q2W cohorts are expected to have higher proportion of subjects (4-5 folds when compared with 3 mg/kg Q3W or 2 mg/kg Q2W) achieving PK exposures associated with better PFS/DoR
- Safety ER analyses didn't demonstrate clinically significant increase in risk when dose increased from 3 to 6 mg/kg Q3W
- Preliminary efficacy, safety and PK/PD data demonstrates favorable benefit risk profile and support future exploration of osemitamab at the recommended dose of 6mg/kg Q3W or 4mg/kg Q2W

Reference and Disclaimer

[1]J Gong et al, 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. ESMO 2022

Lin Shen, chief physician of Peking University Cancer Hospital confirmed that she does not have conflicts of interest to declare on the Poster.

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