Osemitamab (TST001), an ADCC Enhanced Humanized Anti-CLDN18.2 mAb, Demonstrated Improved Efficacy in Combination with Anti-PD-L1/PD-1 mAb and Oxaliplatin/5-FU in Preclinical Tumor Models

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BACKGROUND

- Osemitamab (TST001) is a best-in-class humanized antibody with improved CLDN18.2 binding affinity and ADCC activity.
- Here, we evaluated the dynamics of on-treatment PD-L1 expression on the tumor cells in both *in vivo* tumor models and *in vitro* tumor cells, and studied preclinical efficacy of the combination of Osemitamab and anti-PD-L1/PD-1 mAb +/- oxaliplatin/5-FU (Oxa/5-FU) in both CLDN18.2+/PD-L1+ and CLDN18.2+/PD-L1- PDX tumor models.

METHODS

- For *in vitro* cell assay, we co-cultured the CLDN18.2-expressing GC cells w/wo human PBMC and 30 μg/ml Osemitamab for 72hr, and then transferred the supernatant to the matched tumor cells for another 72hr incubation. PD-L1 expression on the tumor cells was detected using FACS analysis.
- The mouse with CLDN18.2-expressing tumors were injected intraperitoneally with Osemitamab or in combination with anti-PDL1/PD-1 mAbs twice a week and injected intravenously with Oxa/5-FU weekly in *in vivo* efficacy studies. PD-L1 and CD3/CD8 expression on the tumors was detected by using IHC analysis.

Figure 1. Schematic diagram of *in vitro* PD-L1 upregulation assay on GC tumor cells

RESULTS

- We found that in the presence of human immune cells, PD-L1 expression on the CLDN18.2-expressing GC cells *in vitro* and tumors *in vivo* was upregulated after Osemitamab treatment.
- In two CLDN18.2+/PD-L1+ mouse syngeneic models, Osemitamab combined with Atezolizumab exhibited significantly higher tumor growth inhibition (TGI) than the single agents.
- Furthermore, in the CT26 tumor model, the triplet [Osemitamab in combination with anti-mouse PD-1 (RMP1-14) + Oxa/5-FU] showed even better TGI than the doublet [Osemitamab + Oxa/5-FU or RMP1-14 + Oxa/5-FU].
- Additionally, in a CLDN18.2+/PD-L1 negative GC PDX model with human PBMC reconstruction on B-NSG-hIL-15 mice, Osemitamab in combination with Oxa/5-FU and Nivolumab was superior to Oxa/5-FU+Osemitamab or Oxa/5-FU + Nivolumab.

PD-L1 upregulation on CLDN18.2-expressing GC cells by Osemitamab treatment in the presence of human PBMC *in vitro*

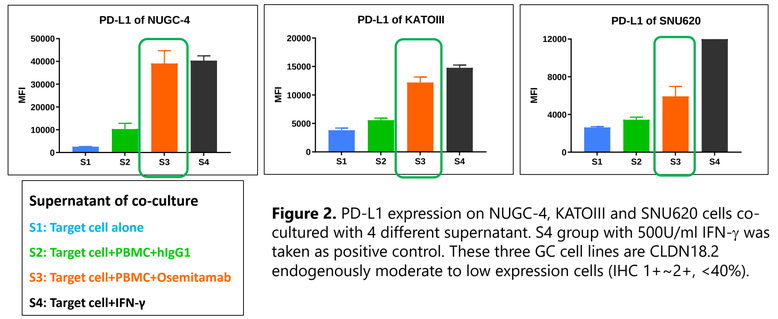

Figure 2. PD-L1 expression on NUGC-4, KATOIII and SNU620 cells co-cultured with 4 different supernatant. S4 group with 500U/ml IFN-γ was taken as positive control. These three GC cell lines are CLDN18.2 endogenously moderate to low expression cells (IHC 1+~2+, <40%).

Increasing of PD-L1 and TIL on CLDN18.2-expressing gastric PDX post Osemitamab treatment *in vivo*

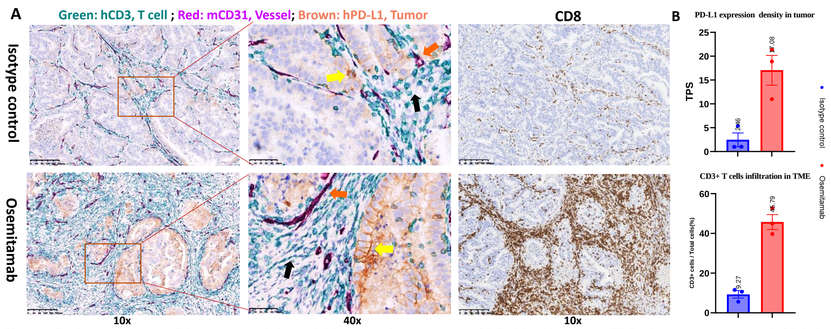

Figure 3. A:multiplex IHC immunostaining of PD-L1 (yellow arrow), CD3 (black arrow), CD31(brown arrow) and CD8 **B:** Quantitative analysis of PD-L1 expression density and CD3 distribution on CLDN18.2-expressing(3+, 95~100%) tumors from human PBMC co-inoculation gastric PDX models. 10mg/kg Isotype control or Osemitamab were intraperitoneally administrated twice a week and tumors were harvested for biomarkers analysis after 3-week treatment.

The combination of Osemitamab and Atezolizumab enhanced anti-tumor effect in CLDN18.2+/PD-L1+ mouse tumor models

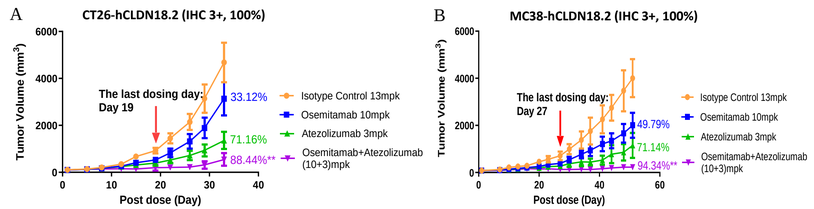

Figure 4. The efficacy study of Osemitamab in combination with Atezolizumab in CLDN18.2+/PD-L1+ mouse tumor models. CT26-hCLDN18.2 and MC38-hCLDN18.2 were stably transfected with human CLDN18.2. Their CLDN18.2 and PD-L1 were tested as positive expression by FACS, and CLDN18.2 IHC scores were shown on titles of each graph. Average tumor volume (±SEM) in mice bearing CT26-hCLDN18.2 tumors (A) or MC38-hCLDN18.2 tumors (B) after Osemitamab, or Atezolizumab, or in combination treatments were measure twice a week. %TGI and statistical significance versus Osemitamab were evaluated for each treatment group (**: vs Osemitamab, P<0.01). The tumor inhibition effect of combination groups lasted for 2 weeks after the last dosing day.

The combination of Osemitamab and RMP1-14 plus Oxa/5-FU enhanced anti-tumor effect in CLDN18.2+/PD-L1+ mouse tumor model

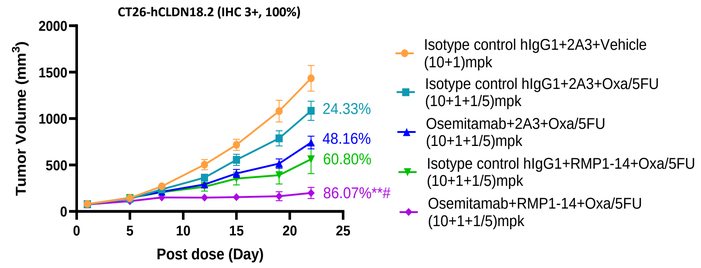

Figure 5. The average tumor volume (±SEM) in mice bearing CT26-hCLDN18.2 tumors after Osemitamab, or RMP1-14+Oxa/5-FU, or in combination treatments. 2A3: Isotype control rat IgG2a; RMP1-14: rat anti-mouse PD-1 monoclonal antibody (**: vs Osemitamab+Oxa/5-FU, P<0.01; #: vs RMP1-14+Oxa/5-FU , P<0.05).

Osemitamab in combination with Oxa/5-FU and Nivolumab was superior to Oxa/5-FU + Osemitamab or Oxa/5-FU + Nivolumab in CLDN18.2+/PD-L1- gastric cancer PDX model

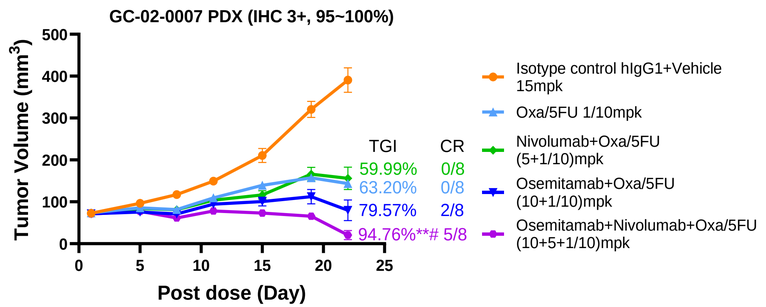

Figure 6. The efficacy study of Osemitamab in combination with chemotherapeutic agents or PD1 inhibitor plus chemotherapy in CLDN18.2-expressing gastric cancer patient derived xenograft (PDX) model. CLDN18.2 IHC score was shown on the tile of graph. (A) Average tumor volume (±SEM) of GC-02-0007 PDX xenograft model with human PBMC injection in the hIL-15 transgenic mice after Oxa/5-FU alone or in combination treatment with Osemitamab or Nivolumab or both. %TGI, complete response (CR) rate and statistical significance of triple combo (Osemitamab, Nivolumab and Oxa/5-FU) versus Nivo+Oxa/5-FU or Osemitamab+Oxa/5-FU were evaluated for each treatment group (**: vs Nivo+Oxa/5-FU, P<0.01; #: vs Osemitamab+Oxa/5-FU, P<0.05).

CONCLUSIONS

- PD-L1 upregulation and increasing of TIL after Osemitamab treatment provided a rationale for combination potential of Osemitamab and anti-PD-L1/PD-1 mAb.
- The synergistic effects of Osemitamab and GC standard of care (SoC: antiPD-1 mAb + Oxa/5-FU) observed in our preclinical tumor models support Osemitamab in combination with SoC chemotherapy +/- Nivolumab in G/GEJ patients regardless of PD-L1 status.

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