Clausen-18 isoform 2 (CLDN18.2) is a member of the human claudin family of tetrameric membrane proteins that are crucial structural and functional components of tight junctions. Unlike other family members, CLDN18.2 expression is strictly limited to differentiated epithelial cells of gastric mucosa (22). Interestingly, CLDN18.2 was ectopically expressed at a significant level in multiple tumor types including gastric, pancreatic, and lung cancers, which makes it an attractive anti-cancer target. 14G11 is a monovalent humanized IgG1 monoclonal antibody, which specifically binds to cells expressing CLDN18.2 with high affinity but not to the closely related Claudin 18.1. TST001 binds to CLDN18.2 via a distinct epitope. By reducing fucosylation during cell culture process, TST001 has further enhanced binding affinity to FcRlIIa, with high potency ADCC activity. Indeed, TST001 showed sub-nanomolar ADCC activity against gastric cancer cells expressing medium to low CLDN18.2 in the presence of human FICM and NK cells, which is significantly more potent than IMAB362 analog. TST001 also showed more potent CDC and ADCC activities against CLDN18.2 expressing cells than IMAB362 analog. In both Sprague Dawley Rat and Cynomolgus Monkey, the systemic exposure of TST001 increased proportionally in a dose-dependent manner. In gastric cancer cell line and patientderived xenograft tumor models, TST001 showed more potent anti-tumor activity as compared with IMAB362 analog. Furthermore, the combination with chemotherapeutic agents resulted in enhanced anti-tumor activity of TST001 in these tumor models. In addition, we have also generated and characterized an antibody that is selective to CLDN18.2 over CLDN18.1 and is suitable for IHC based detection. Altogether, these preclinical findings warrant further clinical evaluation of TST001 in patients with CLDN18.2 expressing tumors.

ABSTRACT

TST001 specifically binds to CLDN18.2

TST001 has a high affinity to both CLDN18.2 and Fc receptors

TST001 has potent killing activities on CLDN18.2-expressing cells

TST001 regresses tumor growth in MKN45-CLDN18.2 xenograft model

About TST001

TST001 is a humanized antibody and produced from a stabilize cell line with low levels of fucose in the Fc region. TST001 has human Fc at position 195, a mouse derived hybridoma antibody. The amino acid 292 of each heavy chain is the conserved N-glycosylation site and post-translation optimization resulted in reduced fucosylation at 292 which enhance the affinity of Fc binding to FcRlIIa and ADCC activity (23).

Chemotherapeutic agents enhances tumor inhibition of TST001

14G11 is selective to CLDN18.2 and suitable for IHC detection

Summary and Conclusions

TST001 displayed specific, high affinity binding to CLDN18.2.

With reduced fucosylation, TST001 has enhanced affinity to FcRlIIa and ADCC activity.

In gastric cancer cell xenograft model, TST001 resulted in tumor regression in a dose-dependent manner.

TST001 combined with chemotherapeutic agent, such as Paclitaxel, resulted in greater tumor inhibition than single agent in a CLDN18.2 positive PDAC model.

TST001 has a linear PK profile and is well tolerated in Cynomolgus monkey.

Antibody 14G11 displayed high specificity and sensitivity to CLDN18.2 in hind limb tumor model and is suitable for IHC detection.

Conclusions: These studies demonstrated that TST001 is capable of potent inducing tumor killing both in vitro and in vivo and warrants further clinical evaluation of TST001 in patients with CLDN18.2 expressing tumors.

Contact email: fei.teng@transcenta.com

Fei Teng1, Yi Gu1, Hui Chai1, Huanhuan Guo1, Hongjun Li1, Xiwen Wu1, Xinlai Yao1, Fei Xu1, Lei Shi1, Zhenzi Yan1, Xiaoli Z1, Zheng Dar1, Timothy Li2, Lisa Zheng1, Francis Fan1, Zhen Yang1, Xueling Qian1.

1Mabspace Biosciences (Suzhou) Co., Limited, Suzhou, China; 2-HUB (Hangzhou) Co, Limited, Hangzhou, China

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Fei Teng1, Yi Gu1, Hui Chai1, Huanhuan Guo1, Hongjun Li1, Xiwen Wu1, Xinlai Yao1, Fei Xu1, Lei Shi1, Zhenzi Yan1, Xiaoli Z1, Zheng Dar1, Timothy Li2, Lisa Zheng1, Francis Fan1, Zhen Yang1, Xueling Qian1.

1Mabspace Biosciences (Suzhou) Co., Limited, Suzhou, China; 2-HUB (Hangzhou) Co, Limited, Hangzhou, China

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The Preclinical Characterization of TST001, A Novel Humanized Anti-Claudin18.2 mAb with Enhanced Binding Affinity and Anti-Tumor Activity

Fei Teng1, Yi Gu1, Hui Chai1, Huanhuan Guo1, Hongjun Li1, Xiwen Wu1, Xinlai Yao1, Fei Xu1, Lei Shi1, Zhenzi Yan1, Xiaoli Z1, Zheng Dar1, Timothy Li2, Lisa Zheng1, Francis Fan1, Zhen Yang1, Xueling Qian1.

1Mabspace Biosciences (Suzhou) Co., Limited, Suzhou, China; 2-HUB (Hangzhou) Co, Limited, Hangzhou, China

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