792 GIVASTOMIG, A NOVEL CLAUDIN18.2/4–1BB BISPECIFIC ANTIBODY, EXERTS BYSTANDER TUMOR-KILLING AND SYNERGISTIC ANTI-TUMOR ACTIVITY WITH THERAPEUTICS IN 1L/2L TREATMENT FOR GASTRIC CANCER

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http://dx.doi.org/10.1136/jitc-2023-SITC2023.0792

Background Givastomig (TJ-CD4B/ABL111) is a first-in-class bispecific antibody designed to target tumors with a wide range of Claudin 18.2 (CLDN18.2) expression and elicit 4–1BB-mediated T cell activation upon engagement with CLDN18.2-expressing tumor cells. Here we further investigate the mechanism of givastomig and explore its potential in combination with first-line (1L) and second-line (2L) therapeutics for gastric cancer.

Methods The CLDN18.2 expression in formalin-fixed, paraffin-embedded (FFPE) tumors of three human gastric cancer cell lines (MKN-45, MKN-45#14, and MKN-45#18; obtained from Genomeditech) was determined by immunohistochemistry (IHC) staining. The T cell activation and tumor-killing mediated by givastomig were investigated, either alone or in combination with other therapies, using a co-culture system of tumor cells and PBMCs. T cell activation was evaluated by the production of INFg, IL2 and soluble 4–1BB, while tumor-killing was evaluated by the CellTiter-Glo® Assay. Anti-tumor activity and pharmacodynamics effects of the combination treatment were also examined by *in vivo* gastric cancer patient-derived xenograft (PDX) model.

Results Based on IHC staining, MKN-45, MKN-45#18, and MKN-45#14 exhibited negative (<10% of 1+), low (65% of 1+, no 2+/3+), and moderate (35% of 1+ and 65% of 2+) CLDN18.2 expression, respectively. Givastomig induced T cell activation in a dose and CLDN18.2 expression dependent manner. Givastomig elicited tumor-killing activity against CLDN18.2-positive MKN-45#14 and MKN-45#18 cells but not CLDN18.2-negative MKN-45 cells. Interestingly, bystander tumor-killing was observed in a mixture of MKN-45#14 cells and MKN-45 cells at various ratios in the presence of givastomig. In addition, givastomig-mediated T cell activation and tumor-killing was enhanced in combination with chemotherapies used in 1L or 2L treatment for gastric cancer, including 5-fluorouracil plus oxaliplatin (FOLFOX) and paclitaxel. In a gastric cancer PDX model with moderate CLDN18.2 expression (25–50% of 2+), a triple-combination of givastomig, nivolumab and FOLFOX resulted in better tumor growth inhibition (TGI=40%), accompanied by an increase in tumor-infiltrating T cells, compared to nivolumab plus FOLFOX (TGI=8%).

Conclusions In an *in vitro* co-culture system that mimics tumor microenvironment, givastomig exerts bystander tumor-killing in which givastomig-mediated T cell activation by CLDN18.2-positive tumor cells leads to the killing of nearby CLDN18.2-negative tumor cells. These results indicate the therapeutic potential of givastomig in the treatment of solid tumors with broad and heterogenous CLDN18.2 expression. The synergistic anti-tumor activity by givastomig in combination with current therapeutics in 1L/2L treatment for gastric cancer, as demonstrated in preclinical studies, warrants further investigation of these combinations in clinics.