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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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 INFγ, 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.

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COMBINED ADMINISTRATION OF THE DUAL A2aR/A2bR ANTAGONIST ETRUMADENANT WITH A REDUCED CHEMOTHERAPY REGIMEN LEADS TO ENHANCED TUMOR EFFICACY AND SURVIVAL

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Background Chemotherapy remains the standard of care for numerous cancer indications; however, in addition to having poor overall tolerability, a negative effect of such regimens is the extracellular release of adenosine triphosphate, which is rapidly converted to immunosuppressive adenosine by the enzymes CD39 and CD73. Extracellular adenosine drives immunosuppression by activating the A2aR and A2bR adenosine receptors on immune cells, thereby inhibiting their activity and enabling tumor growth and survival. We have previously shown that etrumadenant (etruma), a dual A2aR/A2bR antagonist, prevents adenosine-mediated immunosuppression in vitro and combines with immunogenic chemotherapy to enable greater control of mouse syngeneic tumors. In our current work, we sought to evaluate the ability of etruma to enhance the anti-tumor immune activity of priming doses of chemotherapy, compared to an extended chemotherapy regimen alone.

Methods Mice were inoculated with syngeneic cancer cells, 4T1 or AT3-OVA. Once tumors were established (50 or 100 mm³), mice were treated with doxorubicin (5 mg/kg, Q7D), alone or in combination with etruma (100 mg/kg BID). Gross anatomic, histological and flow cytometric analyses of CD8+ T cells were performed on tumor or lung tissue.

Results We have previously shown in AT3-OVA tumors that etruma combines with doxorubicin (dox) to provide greater tumor control and CD8+ T cell infiltration compared to dox alone. Building upon these data, we combined etruma with 2 or 4 doses of dox and found that addition of etruma significantly reduced tumor burden and increased survival in both dox dosing regimens. Etruma combined with 2 dox doses showed similar tumor control as 4 doses of dox alone (2 dose dox: 601 ± 79 mm³; 2 dose combo: 232 ± 25 mm³; 4 dose dox: 263 ± 26 mm³). Similar results were observed in 4T1 tumor-bearing mice, where etruma in combination with dox suppressed lung metastases after 2 doses of dox with no further improvement observed with a third dose of chemotherapy (lung mets per mouse: 3 dose dox: 41 ± 5; 2 dose combo: 16 ± 4; 3 dose combo: 12 ± 2). These data suggest that etruma sustains the immune response driven by the initial doses of chemotherapy leading to enhanced tumor control.

Conclusions Altogether, these data show that the combined treatment of chemotherapy with etruma leads to increased tumor control in multiple preclinical models and suggest that etruma combined with a reduced course of chemotherapy may have comparable activity as an extended chemotherapy dosing regimen.

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