809 ANTI-CLDN18.2 ANTIBODY ZL-1211 ENHANCES ANTI-TUMOR ACTIVITIES IN COMBINATION WITH CHEMOTHERAPY IN GASTRIC CANCER MODELS

Anthony Cao, Qiuping Ye, Karl Hsu, Hua Gong, Haiying Zhou, Jiaqing Yi*, Xinyan Tang. *Zai Lab, Menlo Park, CA, USA*

Background CLDN18 is a member of the claudin family transmembrane proteins expressed at the epithelial tight junctions to establish a paracellular barrier to control the flow of ions and solutes between cells. Localization of the CLDN18.2 isoform is strictly confined to and buried within tight junctions in the gastric mucosa in healthy individuals. During malignant transformation however, CLDN18.2 is overexpressed in up to 60% of gastric cancers, and ectopically expressed in 50% of pancreatic and 30% of esophageal cancers. Anti-CLDN18.2 has shown the potential to inhibit tumor growth alone or in combination with standard of care chemotherapies in gastric cancer.

Methods In vitro antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) assays were used to measure ZL-1211 efficacy. SNU601 xenograft gastric cancer model was used in BALB/c Nude mice to measure the efficacy of ZL-1211 in combination with standard of care (SoC) chemotherapy. RT-qPCR and western blot were used to measure CLDN18.2 expression levels, and ELISA was used to measure cytokine levels.

Results ZL-1211 is an anti-CLDN18.2 IgG1 that possesses enhanced Fc-dependent effector functions to enable potent ADCC, ADCP, and CDC. ZL-1211 increased therapeutic benefit over the most advanced anti-CLDN18.2 antibody benchmark with greater than 10-fold induction of immune effector functions under tested conditions. Chemotherapy, such as gemcitabine, increased CLDN18.2 mRNA and protein expression levels in cancer cells and sensitized tumor cells to ZL-1211-mediated ADCC. Furthermore, ZL-1211 in combination with SoC chemotherapies, oxaliplatin + capecitabine (CAPOX), enhanced anti-tumor efficacy in SNU601 gastric cancer xenograft model. Additionally, ZL-1211 in combination with chemotherapy treatment induced remarkable pro-inflammatory cytokine release, which might associate with its deeper and durable anti-tumor responses.

Conclusions These data provide rationale to combine ZL-1211 with SoC chemotherapy in gastric cancer. Currently, a phase I dose escalation study is underway to assess the safety, tolerability, pharmacodynamics, and pharmacokinetics of ZL-1211 in patients with advanced solid tumors (NCT05065710).

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