COMBINATION OF HER2 ADC AND LEMZOPARLIMAB ELICITS ENHANCED EFFICACY IN BOTH HER2 HIGH-AND LOW-EXPRESSING BREAST AND GASTRIC CANCERS

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Background Lemzoparlimab (also known as TJC4) is a differentiated anti-CD47 antibody with novel epitope and RBC sparing properties. Previous data has shown that CD47 is upregulated preferentially in HER2-expressing cells and dual blockade of CD47 and HER2 increased tumor attack. The combination of lemzoparlimab with HER2 ADC maybe a promising therapy for treating HER2 positive patients. Here, we report the enhanced anti-tumor efficacy of the combination of lemzoparlimab with HER2 ADC in cell derived xenograft (CDX) and patient derived xenograft (PDX) breast and gastric cancer models.

Methods Breast and gastric cancer cell lines with different expression levels of HER2 and CD47 quantified by flow cytometry were selected for this study. In vitro cytotoxicity of RC48 (Disitamab Vedotin), alone or in combination with lemzoparlimab was evaluated in co-culture of human PBMC with tumor cell lines. In vivo activity of RC48 or in-house produced DS8201 analogue in combination with lemzoparlimab were investigated in CDX (HER2 0/1+/3+ by IHC) and PDX (HER2 2+ by IHC) models. Tumor infiltrating leukocytes (TILs) were analyzed by flow cytometry. The expressions of CD47 and CD68 in tumor were measured by immunohistochemistry.

Results In combination with lemzoparlimab in vitro, RC48-mediated cytotoxicity against both BT-474 and MCF-7 cells was enhanced, while the increase in cytotoxicity was more prominent in HER2-low MCF-7 cells than HER2-high BT474 cells. In vivo combination treatment of DS8201 analogue or RC48 with lemzoparlimab exhibited stronger anti-tumor efficacy compared with monotherapy in both CDX and PDX models with different levels of HER2 expression. The synergistic efficacy by combination treatment was more pronounced in tumor with HER2-low expression than that with HER2-high expression. Treatment effect in tumor microenvironment by RC48 and lemzoparlimab was further investigated. Compared to RC48 monotherapy, RC48 combined with lemzoparlimab significantly up-regulated the percentage of activated and total NK cells, CD68+ macrophages and the ratio of M1/M2 macrophage in TILs (p<0.05 in all comparisons). In addition, the CD47 expression in tumor cells was also increased by the combination treatment.

Conclusions This study demonstrated the synergistic effect of combining CD47 blocker and HER2 ADC in tumors with different levels of HER2 expression. Lemzoparlimab potentiated HER2 ADC mediated tumor killing by modulating NK cells and macrophage activity to increase cytotoxicity and phagocytosis. These data support future clinical investigation of lemzoparlimab and HER2 ADC combination in HER2 positive patients, especially those with HER2-low expressing tumors.