821 **THE COMBINATION OF A TRASTUZUMAB ISAC AND PERTUZUMAB AUGMENTS ANTI-TUMOR EFFICACY IN MULTIPLE HER2+ TUMOR MODELS RELATIVE TO TRASTUZUMAB PLUS PERTUZUMAB**

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**Background** Immune-stimulating antibody conjugates (ISACs) are comprised of immune stimulants conjugated to tumor-targeting antibodies. Trastuzumab-T785 ISAC is a murine surrogate of BDC-1001, a HER2-targeting ISAC currently under evaluation in Phase 2 studies. Trastuzumab-T785 consists of trastuzumab conjugated with a non-cleavable linker to a TLR7/8 agonist. Trastuzumab-T785 elicits myeloid activation and tumor eradication in trastuzumab-resistant HER2 IHC3+ models. Given that the activity of trastuzumab-T785 is dependent on FcgR-mediated phagocytosis, we hypothesized that trastuzumab-T785 and pertuzumab, which binds a distinct HER2 epitope from trastuzumab, would enhance anti-tumor efficacy by increasing Fc clustering and promoting phagocytosis.

**Methods** The effect of combining pertuzumab with ISAC therapy was explored in nine different xenograft tumor models. SCID/beige mice bearing HER2-expressing tumors (IHC3+, 2+, or 1+) were treated with trastuzumab-T785 at multiple dose levels administered Q5Dx4 in combination with pertuzumab or an isotype control; tumor growth inhibition (TGI) was assessed approximately 20 days after the initial treatment. Intra-tumoral cytokines and chemokines were measured using multiplex ELISA to examine myeloid activation. The role of phagocytes was assessed through in vivo depletion with an anti-CSF1R antibody. The requirement of Fc-mediated effector function was explored using a pertuzumab variant containing Fc effector-attenuating substitutions.

**Results** Trastuzumab-T785 ISAC monotherapy improved TGI compared to trastuzumab and pertuzumab combination, and trastuzumab-T785 and pertuzumab combination further enhanced TGI across multiple tumor models and dose levels. Moreover, the addition of pertuzumab lowered the quantity of ISAC required for efficacy in the JIMT-1 HER2 IHC2+ model. Anti-tumor efficacy depended on phagocytes, as depletion with an anti-CSF1R antibody significantly reduced TGI by ~50%. Treatment with ISAC and a pertuzumab variant with a non-functional Fc region also reduced TGI by ~50%, demonstrating a functional Fc was required for optimal efficacy. The combination of pertuzumab with trastuzumab-T785 ISAC significantly increased the amplitude of the cytokine and chemokine response relative to ISAC monotherapy or antibody combination therapy, indicating enhanced myeloid activation in the tumor.

**Conclusions** The combination of trastuzumab-T785 and pertuzumab significantly enhanced efficacy in multiple HER2-expressing tumors, including those with lower HER2 expression. ISAC therapy utilizes phagocytosis to initiate anti-tumor responses, and pertuzumab serves as an additional source of 'eat me' signals that likely enhance phagocytosis and deepen anti-tumor efficacy. These studies suggest that this combination may enhance the clinical activity of trastuzumab-based ISACs. This hypothesis is being assessed in a randomized Phase 2 clinical trial with BDC-1001 and pertuzumab in patients with HER2+ breast cancer post trastuzumab deruxtecan (BBI-20231001).