813 COMBINATION OF HEXABODY-CD27 WITH PD-(L)1 BLOCKADE POTENTIATES SINGLE-AGENT ACTIVITY LEADING TO ENHANCED HUMAN T-CELL EFFECTOR FUNCTIONS *IN VITRO*

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Background Activation of the T-cell co-stimulatory receptor CD27 and blockade of the PD-1:PD-L1 axis can augment antitumor immune responses through distinct mechanisms. HexaBody®-CD27 (GEN1053/BNT313) is a novel CD27 human monoclonal antibody with a functionally inert IgG1 Fc domain harboring a hexamerization-enhancing mutation to induce CD27 activation independently of Fc gamma receptor crosslinking, while also avoiding T-cell depletion. This unique mechanism of action distinguishes HexaBody-CD27 from other CD27-targeting monoclonal antibodies. In preclinical studies, HexaBody-CD27 enhanced proliferation and effector functions of activated T cells.

Methods The effects of combining HexaBody-CD27 with anti-PD-(L)1 antibodies (pembrolizumab, nivolumab, and atezolizumab) on human $CD8^+$ T-cell proliferation and effector functions were investigated *in vitro*. $CD8^+$ T-cell proliferation and cytokine secretion were assessed in an antigen-specific assay using claudin-6 as a model antigen. Cytotoxic activity of claudin-6-specific human $CD8^+$ T cells towards MDA-MB-231 tumor cells expressing cognate antigen was analyzed using real-time analysis of tumor cell mass, along with flow cytometric analysis of granzyme B and CD107a expression on $CD8^+$ T cells. The effect of combining HexaBody-CD27 with pembrolizumab on IFN-γ secretion was evaluated in a mixed lymphocyte reaction (MLR) assay, with synergy analysis using the Highest Single Agent model.

Results Combination treatment with HexaBody-CD27 and all tested anti-PD-(L)1 antibodies enhanced proliferation and proinflammatory cytokine secretion of antigen-specific $CD8^+$ T cells in coculture with cognate antigen-expressing dendritic cells, compared to the respective single-agent treatments. Furthermore, the combination increased granzyme B and CD107a expression by antigen-specific $CD8^+$ T-cells and enhanced $CD8^+$ T-cell-mediated cytotoxic activity towards cognate antigen-expressing tumor cells. In MLR assays of human $CD8^+$ T cells and allogeneic dendritic cells, the combination of HexaBody-CD27 and pembrolizumab synergistically enhanced IFN-γ secretion.

Conclusions The combination of HexaBody-CD27 with anti-PD-(L)1 antibodies potentiates the effects of each single agent on effector functions of antigen-specific T cells *in vitro*. This study provides preclinical rationale for investigation of this combination in clinical trials. HexaBody-CD27 is currently being evaluated in patients with advanced solid tumors (NCT05435339).

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