Preclinical characterization of BGB-B3227, a MUC1 x CD16A bispecific engager, for the treatment of MUC1-expressing solid tumors

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Abstract

Background: MUC1 is frequently overexpressed in various human epithelial cancers, including NSCLC, gastrointestinal, breast, pancreatic, ovarian, and colon carcinomas. Despite the development of MUC1 targeted therapies, none have shown significant clinical efficacy. BGB-B3227, a novel bispecific antibody targeting MUC1 and CD16A, is designed to induce NK cell activation and subsequent cytotoxicity against MUC1-expressing tumor cells. Methods: The target binding activity of BGB-B3227 was characterized using biochemical and cell-based assays. The ability of BGB-B3227 to avoid the interference from soluble MUC1 was assessed by a competitive FACS assay. The ADCC and ADCP activities of BGB-B3227 were evaluated in co-culture systems consisting of effector cells and tumor cells expressing varying levels of MUC1, both in the presence and absence of human IgG proteins. Furthermore, the in vivo anti-tumor efficacy of BGB-B3227, both as a monotherapy and in combination with anti-PD-1 antibody, was evaluated in the MC-38/hMUC1X model in human CD16A knock-in mice.Results: BGB-B3227 demonstrated high binding affinity to recombinant human CD16A protein and CD16A expressing cells, with comparable binding affinities to both CD16A-158V and 158F variants. BGB-B3227 displayed no detectable binding to either human CD16B NA1 (A) and NA2 variants, underscoring its high selectivity for CD16A. Additionally, BGB-3227 demonstrated high binding affinity to the recombinant SEA domain of human MUC1 protein and MUC1 expressing tumor cells. Compared to HMFG1, which targets MUC1-N, the BGB-B3227's binding to MUC1 expressing cells was less interfered by soluble MUC1. In cellular assays, BGB-B3227 induced potent ADCC and ADCP activity against MUC1-expressing cells in a dose-dependent manner, which was greater than that of Fc-enhanced mAb and was less affected by human IgG. No activity was observed in MUC1-negative tumor cells, indicating the effect of BGB-B3227 is MUC1 dependent. In mouse models, BGB-B3227 monotherapy demonstrated a dose-dependent anti-tumor efficacy, which was further enhanced when combining with an anti-PD-1 antibody. Importantly, no significant changes in animal body weight were observed across all treatments, suggesting good tolerability of BGB-B3227 in mouse models. Conclusion: BGB-B3227 is a bispecific MUC1xCD16A NK engager demonstrating potent ADCC and ADCP activity, along with notable in-vivo anti-tumor efficacy when used as a monotherapy or in combination with anti-PD-1 therapy. BGB-B3227 represents a promise therapeutic option for MUC1-expressing cancers, with the potential to overcome the limitations of MUC1-N antibodies by mitigating the sink effect from soluble MUC1. Currently, BGB-B3227 alone and in combination with Tislelizumab is under clinical investigation in participants with advanced or metastatic solid tumors (NCT06540066).