BGB-A425: a humanized anti-human Tim-3 antibody that exhibits strong immune cell activation

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Abstract

Background: Tim-3 (T-cell immunoglobin and mucin-domian containing-3) is a “checkpoint” inhibitory receptor , which is primarily expressed in activated or “exhausted” T cells, NK cells, macrophages and DCs. Engagement of Tim-3 receptor by its ligand phosphatidylserine (PtdSer) or galectin-9 leads to activation of negative regulatory signaling in T-cells, promoting functional exhaustion of tumor-infiltrating T-lymphocytes. BGB-A425 is a novel humanized IgG1 (variant) anti-T im-3 antibody under preclinical development. The immunomodulatory activity of BGB-A425 was evaluated both in vitro and in vivo.

Materials and methods: BGB-A425 was generated through hybridoma fusion, humanized by CDR grafting and structural simulation. The Fc region (IgG1) of BGB-A425 was engineered to remove Fc gamma receptor (FcγR) binding. The binding affinity and specificity were studied by ELISA, FACS and SPR (Biacore). The immunomodulatory functions of BGB-A425 were evaluated using primary immune cells as well as cell lines.

Results: BGB-A425 binds to the extracellular domain of human Tim-3 with high affinity (K = 0.36 nM) and specificity. In a competition assay, BGB-A425 efficiently blocks the interactions between Tim-3 and PtdSer. In vitro, BGB-A425 significantly enhances IFN-γ production of primary T cells and NK-mediated cytotoxicity against tumor cells. In a MLR assay, BGB-A425 augments T-cell response to allogeneic antigens either alone or in combination with an anti-PD-1 antibody BGB-A317. Besides blocking Tim-3, BGB-A425 can also induce the internalization of Tim-3 receptor on cell surface. In vivo, BGB-A425 in combination with BGB-A317 inhibits tumor growth in a mouse xenograft cancer model.

Conclusions: BGB-A425 demonstrates potent activity to stimulate immune cell function both in vitro and in vivo, supporting its clinical development for the treatment of human cancers.