**Title: A Fc-competent anti-human TIGIT blocking antibody BGB-A1217 elicits strong immune responses and potent anti-tumor efficacy in pre-clinical models**

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**Background:** TIGIT (T-cell immunoglobulin and ITIM domain) is a "checkpoint" inhibitory receptor, which is primarily expressed on activated and "exhausted" T and NK cells. Engagement of TIGIT to its ligands (i.e., PVR and PVR-L2) leads to inhibitory signaling in T cells, promoting functional exhaustion of tumor-infiltrating T lymphocytes. BGB-A1217 is a novel humanized IgG1 anti-TIGIT antibody under clinical development. The immunomodulatory activity of BGB-A1217 was evaluated both *in vitro* and *in vivo*.

**Materials and methods:** BGB-A1217 was generated through hybridoma fusion, humanized by CDR grafting and structural simulation. The binding affinity and specificity were studied by FACS and SPR. The immunomodulatory functions of BGB-A1217 were evaluated using primary immune cells as well as using animal models.

**Results:** BGB-A1217 binds to the extracellular domain of human TIGIT with high affinity ($K_D$ = 0.135 nM) and specificity. In a competition assay, BGB-A1217 efficiently blocks the interaction between TIGIT and PVR. *In vitro,* BGB-A1217 significantly enhances T-cell functions and induces potential ADCC against $TIGIT^{Hi}$ targets. In a human T-cell assay, BGB-A1217 enhances IFN-γ production of CMV-specific T cells. In a PBMC assay, BGB-A1217 augments T cell response, either alone or in combination with an anti-PD-1 antibody BGB-A317. Besides blocking TIGIT signaling, BGB-A1217 can also remove TIGIT from cell surface through trogocytosis. This activity is Fc-dependent. *In vivo*, the Fc effector function is critical for the activity of BGB-A1217 against CT26WT tumor implanted in humanized TIGIT knock-in mice. The observed anti-tumor efficacy is associated with pharmacodynamic change of TIGIT down-regulation, CD226 upregulation and Treg depletion at 48hrs after first dosing.

**Conclusions**: BGB-A1217, either alone or in combination with anti-PD-1 mAb promotes immune cell activation both *in vitro* and *in vivo*, supporting its clinical development for the treatment of human cancers.