A DIFFERENTIATED ANTI-OX40 AGONIST BGB-A445
DOES NOT BLOCK OX40-OX40L INTERACTION AND REVEALS REMARKABLE ANTI-TUMOR EFFICACY IN PRECLINICAL MODELS

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Background
OX40 is a member of the tumor necrosis factor receptor super family (TNFRSF) primarily expressed on activated CD4+ and CD8+ T cells, as well as natural killer (NK) T and NK cells. It is an immune costimulatory receptor which activated CD4+ and CD8+ T cells, as well as natural killer (NK) cells. It is an immune costimulatory receptor which binds to its ligand OX40L and activates downstream NF-kB pathway to induce immune cell activation, proliferation, and survival. Current agonistic anti-OX40 antibodies in clinic, which are mostly ligand-competitive antibodies, showed limited clinical responses, mainly at lower doses. Blockade of OX40-OX40L interaction might limit the efficacy of these ligand-competitive antibodies at higher doses, as OX40-OX40L interaction is essential for enhancing effective anti-tumor immunity. Here we report pre-clinical data of BGB-A445, which is a ligand non-blocking agonistic anti-OX40 humanized antibody.

Methods
Cell-based flow cytometry assay was established to determine whether BGB-A445 interferes with OX40-OX40L interaction. Co-crystal structure of OX40/BGB-A445 Fab was solved to study the molecular binding mechanism. A mixed lymphocyte reaction (MLR) assay was set up to investigate the ability of BGB-A445 to activate CD4+ T-cells. The anti-tumor efficacy of BGB-A445 was evaluated in MC38 colon cancer and CT26WT colon cancer models either as a single agent or in combination with anti-PD-1 antibody.

Results
The flow cytometry study showed that BGB-A445 did not interfere with the binding of OX40 to OX40L even at high concentrations. In contrast, MOXR0916, an anti-OX40 agonistic antibody developed by Genentech, completely blocked OX40 binding to OX40L. Additionally, the co-crystal structure of OX40/BGB-A445 Fab complex indicated that BGB-A445 interacts with the CRD4 region of OX40 which is distant from OX40L binding region. In the MLR assay, combined with an anti-PD-1 antibody, BGB-A445 co-stimulated CD4+ T-cells to secrete IL-2 dose-dependently, while MOXR0916 did not. In the MC38 colon cancer model in human OX40 knock-in mice, BGB-A445 demonstrated remarkable anti-tumor efficacy in a dose-dependent manner, while MOXR0916 showed a 'hook effect' in the same setting. In addition, BGB-A445 exhibited significant anti-tumor activity in the PAN02 pancreatic model which is resistant to anti-PD-1 treatment. Besides, BGB-A445 revealed significant combination effects with anti-PD-1 therapy in both MC38 and CT26WT models.

Conclusions
In conclusion, differentiated from current clinical stage anti-OX40 antibodies, BGB-A445 is an agonistic antibody that does not block the OX40-OX40L interaction. Both in vitro and in vivo results demonstrated that BGB-A445 has remarkable immune stimulating effect and anti-tumor efficacy either as a single agent or in combination with anti-PD-1 therapy, thus warranting further clinical investigation.

REFERENCES