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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

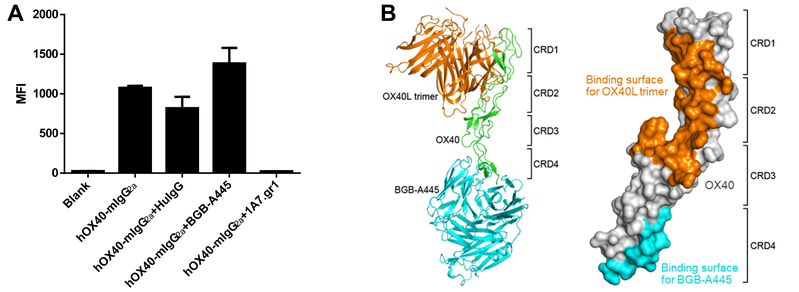
- OX40 is a member of the tumor necrosis factor receptor super family (TNFRSF) primarily expressed on activated CD4⁺ and CD8⁺ T cells, as well as natural killer (NK) T and NK cells.
- OX40 is an immune costimulatory receptor which binds to its ligand OX40L and activates downstream NF-κB pathway to induce immune cell activation, proliferation, and survival [1-3].
- 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.

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, CT26WT and PAN02 syngeneic tumor models in human OX40 knock-in (huOX40) mice either as a single agent or in combination with anti-PD-1 antibody.

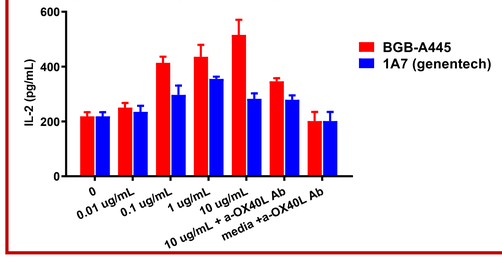
Results

Different from Genentech anti-OX40 mAb, BGB-A445 does not block the OX40-OX40L interaction



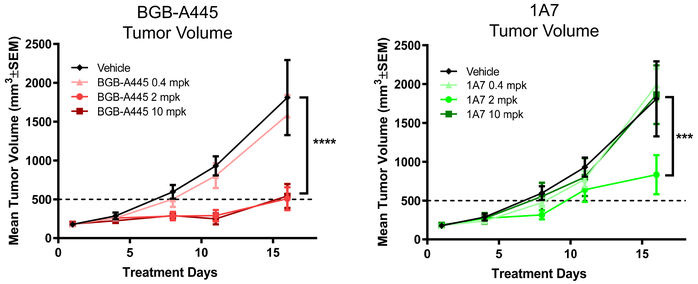
A, BGB-A445 does not interfere with the binding of OX40 to OX40L in cell-based flow cytometry assay. OX40L-expressing HEK293/OX40L cells were incubated with human OX40 fusion protein with murine IgG_{2a} Fc (hOX40-mIgG_{2a}) in the presence of BGB-A445, reference antibody 1A7.gr1 (Genentech), control huIgG or medium alone. The binding of OX40 antibody/OX40 mIgG_{2a} complex to surface OX40L was detected using an anti-mouse Fc secondary antibody. **B**, Crystal structure of OX40/BGB-A445 Fab complex and alignment with the reported OX40/OX40L complex (PDB code: 2HEV). BGB-A445 interacts with the CRD4 region of OX40 which is distant from OX40L binding region.

BGB-A445 promotes immune responses in mixed lymphocyte reaction assay dose-dependently, attributed to its non-ligand competing property



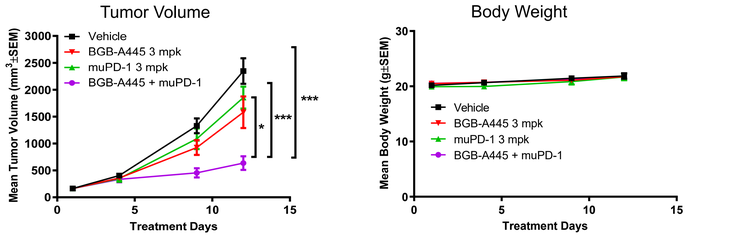
In vitro differentiated dendritic cells (DC) were co-cultured with allogeneic CD4+ T cells in the presence of anti-OX40 antibodies for 2 days. IL-2 in the supernatant was detected by ELISA. All tests were performed in quadruplicates and results were shown as mean ± SEM.

BGB-A445 exerts dose-dependent anti-tumor activity in MC38 colon tumor model, differentiated from 1A7 (Genentech)



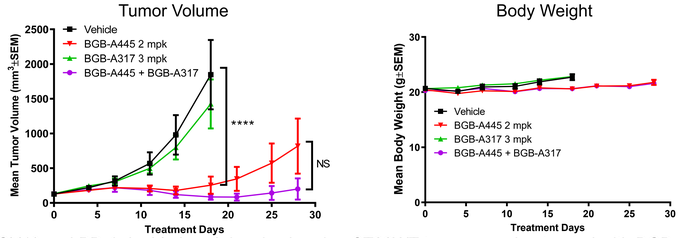
HuOX40 mice bearing MC38 tumor were intraperitoneally (i.p.) treated with either BGB-A445 or 1A7 (Genentech) once a week at indicated doses. Tumor volumes and mice body weight were measured twice weekly. N = 8 per group. *** means P<0.001, **** means P<0.0001. There is no significant change on animal body weight (data not shown).

BGB-A445 shows potent synergistic anti-tumor activity in combination with an anti-PD-1 antibody in MC38 colon tumor model



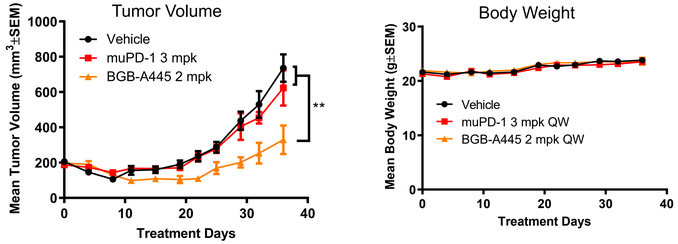
HuOX40 mice bearing MC38 tumor were i.p. treated with BGB-A445, anti-mouse PD-1 antibody, or the combination of the two agents once a week, respectively. N=9 per group. * means P<0.05, *** means P<0.001. The combination of BGB-A445 and anti-PD-1 Ab doesn't have significant effect on animal body weight or any sign of toxicity compared with either single agent.

BGB-A445 in combination with anti-PD-1 antibody reveals better anti-tumor activity than either single agent in CT26WT colon tumor model



Human OX40 and PD-1 double knock-in mice bearing CT26WT tumor were i.p. treated with BGB-A445, BGB-A317 (anti-human PD-1 Ab), or the combination of the two agents once a week, respectively. N=9 per group. **** means P<0.0001. The combination of BGB-A445 and anti-PD-1 Ab doesn't have significant effect on animal body weight or any sign of toxicity compared with either single agent.

BGB-A445 exhibits significant anti-tumor activity in the PAN02 pancreatic model which is resistant to anti-PD-1 treatment



HuOX40 mice bearing Pan02 tumor were i.p. treated with either BGB-A445 or anti-mouse PD-1 antibody once a week at indicated doses. N=9 per group. ** means P<0.01. There is no significant change on animal body weight.

Conclusions

- Differentiated from current clinical stage anti-OX40 antibodies, BGB-A445 is an agonistic antibody that does not block the OX40-OX40L interaction.
- BGB-A445 shows significant immune stimulating effect *in vitro*.
- BGB-A445 has distinctive anti-tumor efficacy either as a single agent or in combination with anti-PD-1 therapy *in vivo*.
- BGB-A445 also exhibits significant anti-tumor efficacy in the PAN02 pancreatic model which is resistant to anti-PD-1 treatment.

References

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