

A differentiated anti-OX40 agonist BGB-A445 does not block OX40-OX40L interaction and reveals remarkable anti-tumor efficacy in preclinical models

Ye Liu, Beibei Jiang, Tong Zhang, Zuobai Wang, Yingcai Feng, Haiying Li, Wenfeng Gong, Xing Wang, Yajuan Gao, Xiaosui Zhou, Bo Zhang, Yuan Hong, Jing Wang, Zilin Wang, Hongjia Hou, Hanzi Sun, Xiaomin Song, Kang Li and Xuesong Liu. BeGene (Beijing) Co., Ltd., Beijing, China

Abstract

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 binds to its ligand OX40L and activates downstream NF- κ B 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. 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

1. Croft M. Control of immunity by the TNFR-related molecule OX40 (CD134). *Annu Rev Immunol* 2010;**28**:57–78.
2. Gramaglia I, et al. Ox-40 ligand: a potent costimulatory molecule for sustaining primary CD4 T cell responses. *J Immunol* 1998;**161**:6510–6517.
3. Song J, So T, Croft M. Activation of NF-kappaB1 by OX40 contributes to antigen-driven T cell expansion and survival. *J Immunol* 2008;**180**:7240–7248.