BGB-B167, a first-in-class 4-1BB/CEACAM5 bispecific antibody, exhibits potent in vitro and in vivo antitumor activity and superior safety profile in preclinical models

Zhuo Li#, Liang Qu, Xin Chen, Liu Xue, Jie Li, Qi Liu, Jian Sun, Hanzi Sun, Yun Chen, Yuanyuan Xie, Wanyi Wang, Lin Zhu, Penghao Wang, Xiaosui Zhou, Hongjia Hou, Jie Chen, Xinyi Liu, Yilu Zhang, Ning Liu, Xinyi Liang, Shuo Zhang, Mingming Guo, Xiaoyan Tang, Jing Song, Tong Zhang, Xiaomin Song, Xuesong Liu, Kang Li, Chichi Huang#

Authors' Affiliation: BeiGene Global Research, P.R. China; #Correspondence: zhuo.li@beigene.com, chichi.huang@beigene.com

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Abstract

4-1BB (CD137) is a key costimulatory immunoreceptor and a promising therapeutic target in cancer. CEACAM5 (CEA) is a well-established tumor-associated antigen overexpressed in many cancers, including colorectal, gastric, lung, pancreatic, liver, breast, and thyroid cancers. BGB-B167 is a novel immunoglobulin G (IgG)-based bispecific antibody targeting 4-1BB and CEA and is under clinical development for the treatment of advanced or metastatic solid tumors in humans.

BGB-B167 binds to its target proteins with high specificity and affinity. Potent and CEA-dependent functional activities are demonstrated using the peripheral blood mononuclear cell (PBMC)-based immune cell activation and cytotoxicity assays. In humanized 4-1BB knock-in mice bearing human CEA-expressing tumors, BGB-B167 exhibits potent, dose-associated single-agent efficacy as well as synergistic antitumor activity in combination with anti PD-1 antibody. BGB-B167 is well-tolerated in 1-month repeat-dose toxicology study in cynomolgus monkeys.

Here, we describe the characterization of BGB-B167 with regard to preclinical proof-of-concept and basic drug-like properties. The combined dataset provides an overview on the design, mode of action, preclinical pharmacology, and safety profile of BGB-B167.

Molecule Design

BGB-B167 is a novel IgG-based bispecific antibody (BsAb) targeting CEA and 4-1BB. It includes a bivalent F(ab')2 fragment that binds to CEA, a fusion of 4-1BB-binding heavy chain variable (VH) domain fragments, and an engineered Fc region that prevents binding to FcγRs (**Figure 1**). BGB-B167 can only cross-link with a 4-1BB receptor when CEA is present, thus resulting in the immune cell stimulation in the tumor microenvironment while greatly reducing risk of systemic toxicity (**Figure 2**).

Figure 1. BsAb design

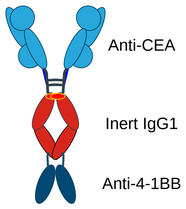
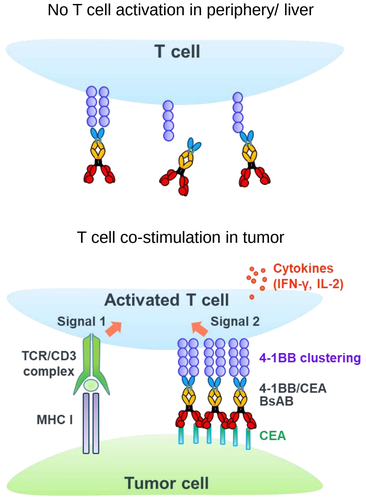
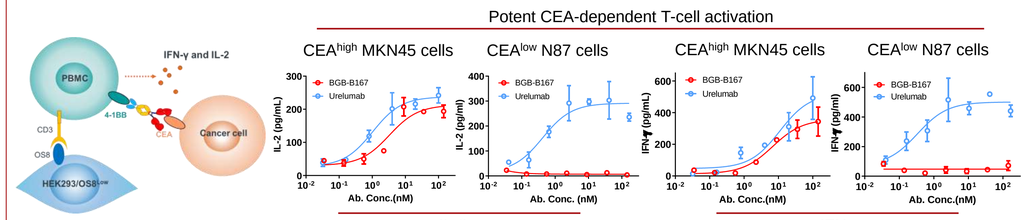


Figure 2. Mechanism of action



Enhanced IFN-γ and IL-2 Secretion from PBMCs in CEA-Dependent Manner

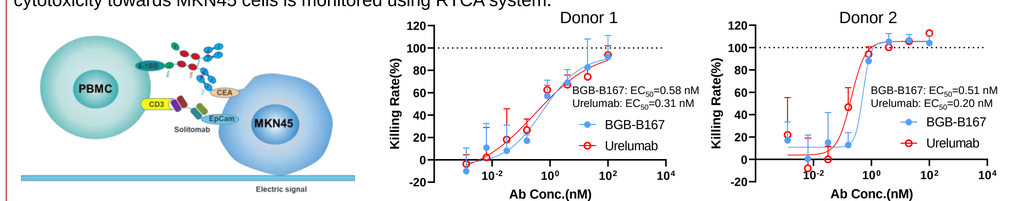
Figure 3. PBMCs are co-cultured with Hek293/OS8low and MKN45 or NCI-N87 cells in the presence of serial diluted BGB-B167 or urelumab. IFN-γ and IL-2 secretions are measured using ELISA.



Data are shown as mean ± SD. hIgG1, human immunoglobulin 1; IFN-γ, interferon-γ; IL-2, interleukin-2.

Potent Cytotoxicity of PBMCs Against Cancer Cells

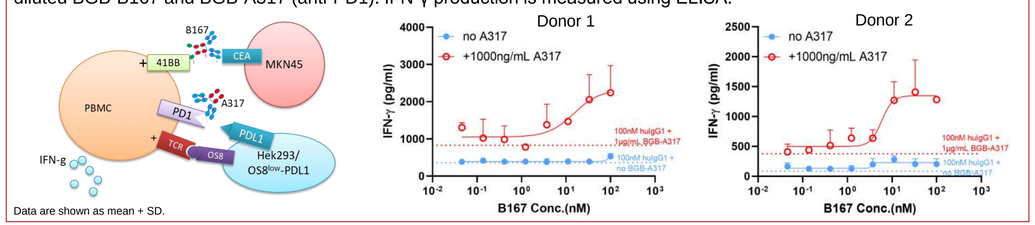
Figure 4. MKN45 cells are pre-cultured to allow cells to adhere to the plate and then co-cultured with PBMCs in presence of BGB-B167 or urelumab. Minimal Solitomab is added into the co-culture system to facilitate initial T-cell activation. The cytotoxicity towards MKN45 cells is monitored using RTCA system.



Cytotoxicity rate (%) is calculated from cell index readout as follows: $Cytotoxicity\ Rate\ (\%) = 100 - \frac{Cell\ Index_{Sample}}{Cell\ Index_{No\ Ab}} \times 100$. EC_{50}, half maximal effective concentration; RTCA, real-time cell analysis.

Combination with Anti-PD1 Ab Promotes IFN-γ Secretion from PBMCs

Figure 5. Pre-stimulated PBMCs are co-cultured with the Hek293/OS8-PD-L1 cells and MKN45 cells in the presence of serial diluted BGB-B167 and BGB-A317 (anti-PD1). IFN-γ production is measured using ELISA.



Data are shown as mean + SD.

Dose-Dependent Antitumor Monotherapy Activity in Human 4-1BB Knock-in Mice

Figure 6. MC38/hCEA cells are implanted into human 4-1BB knock-in mice. BGB-B167 significantly inhibits tumor growth in the MC38/hCEA model; tumor-free rate at study end is 20%, 30%, and 90% for 0.1, 0.5, and 3.0 mg/kg treatment group.

Significant tumor growth inhibition

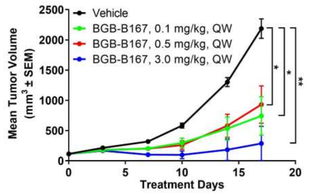
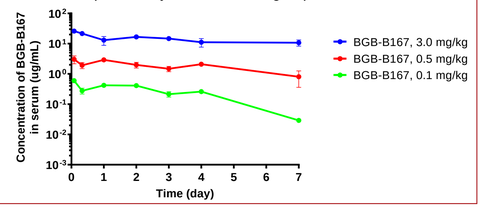


Figure 7. MC38/hCEA tumor bearing human 4-1BB knock-in mice are treated with BGB-B167. Serum concentration is quantified by ELISA. MC38/hCEA model, human CEA expressed in mouse colon adenocarcinoma cell line MC38.

Proportionally increased drug exposure



Enhanced Antitumor Activity when Combined with Anti-PD1 Ab

CT26/hCEA or B16-F10/hCEA cells are implanted into human 4-1BB knock-in mice. The mice are treated with BGB-B167, anti-mouse PD-1 antibody Ch15mt, or a combination of both.

Figure 8. Tumor growth inhibition in combination group is significantly higher in CT26/hCEA model

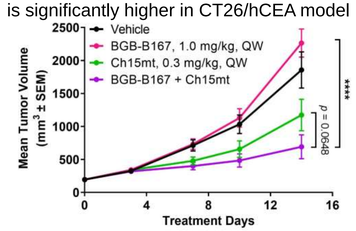
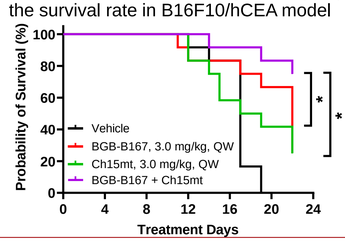


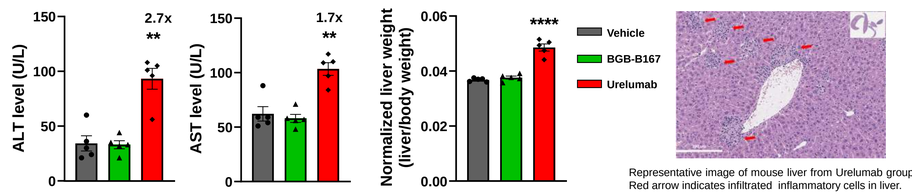
Figure 9. Combination treatment significantly improves the survival rate in B16F10/hCEA model



No Obvious Adverse Effects at 30 mg/kg in Human 4-1BB Knock-in Mice

Figure 10. Human 4-1BB knock-in mice are treated with BGB-B167 and Urelumab analog at 30 mg/kg once weekly for three weeks.

- High-dose Urelumab analog, but not BGB-B167, significantly increases the alanine transaminase (ALT) and aspartate aminotransferase (AST) concentrations.
- Enlarged liver in Urelumab treated group during necropsy, which is consistent with liver weight increase.
- Histopathology examination shows moderate diffused inflammatory cell infiltration in Urelumab treated group.

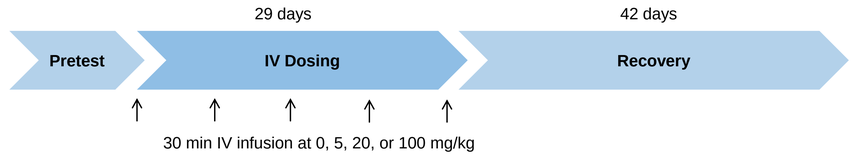


Representative image of mouse liver from Urelumab group. Red arrow indicates infiltrated inflammatory cells in liver.

Well-Tolerated in Non-Human Primate Toxicology Study

Figure 11. The repeat-dose toxicity of BGB-B167 is investigated in a GLP-compliance cynomolgus monkey study.

- BGB-B167 is administered at 0, 5, 20, or 100 mg/kg once weekly for 5 doses via intravenous infusion of approximately 30 min, followed by a recovery period.
- BGB-B167 is well-tolerated at all dose levels, with no significant findings.
- TK analysis demonstrates dose-proportional exposure.
- NOAEL is determined as 100 mg/kg.



Conclusion

BGB-B167 is a selective CEA-dependent 4-1BB targeting bispecific antibody with strong scientific rationale and preclinical proof-of-concept. It demonstrates strong antitumor effects either as mono or in combination with anti-PD1 antibody with a large therapeutic window in pre-clinical setting.

- CEA-dependent T-cell activation and strong antitumor effects in vivo.
- Silenced Fc and thus CEA-dependent 4-1BB activation to avoid peripheral and liver toxicity.
- Enhanced antitumor activity in combination with anti-PD1 antibody.