Discovery of BGB-R046, an IL-15 pro-drug that is conditionally activated by proteases in the tumor microenvironment for the treatment of cancer

Authors: Xudong Luan[1], Zhu Mei[1], Huixia Hu[1], Jing Wang[1], Ying Ma[1], Xiao Yang[1], Min He[1], Xinyi Liang[1], Yanbing Hao[1], Yanwen Ma[1], Chang Song[1], Yue Wu[1], Mengjia Wang[1], Yue Zheng[1], Sean Lin[1], Zhuo Li[1], Mingchao Kang[1], Xiaomin Song[1], Fan Wang[1], Xi Wu[1], Zhirong Shen[1], Chichi Huang[2], Shen Yu[1], Xuesong Liu[1], Xiaodong Wang[1] and Lai Wang[1]

Affiliations: [1]BeiGene, Beijing, China; [2]BeiGene USA, Tallahassee, FL, USA

ABSTRACT

Background: IL-15 is a promising cytokine for cancer immunotherapy as it preferentially promotes natural killer (NK) and $CD8^+$ T-cell expansion. However, the clinical use of IL-15 remains limited due to systemic toxicities and narrow therapeutic window. To overcome these limitations, BGB-R046 was developed as an IL-15 pro-drug, which remains inactive in circulation and can be specifically activated at tumor site by utilizing the tumor enriched protease. BGB-R046 is composed of IL-15Rα-sushi-IL-15, also named the IL-15 superagonist, a protease activatable linker and a masking moiety fused with Fc to extend half-life. Upon activation, IL-15Rα-sushi-IL-15 has natural IL-15 potency and can be quickly cleared due to lack of Fc fusion. Minimal active IL-15Rα-sushi-IL-15 accumulation in circulation may lead to low systemic toxicity and increased therapeutic window.

Methods: The potency of activated BGB-R046 were characterized in both cellular assay and mouse HH cell xenograft model. Anti-tumor efficacy was evaluated in MC38 and B16F10 syngeneic models in IL-15 and IL-15 receptors humanized mice. The pharmacokinetics (PK) and safety profile of BGB-R046 was evaluated in cynomolgus (cyno) monkeys.

Results: Pro-drug (BGB-R046) exhibited relatively low IL-15 activity, and full IL-15 activity was recovered with protease digestion in human cell line and peripheral blood mononuclear cells (PBMC). BGB-R046 was cleaved in tumor microenvironment to release active IL-15Rα-sushi-IL-15 with dose-dependent pharmacodynamics effect in HH xenograft model. BGB-R046 alone or combined with PD-1 antibodies, showed dose dependent antitumor efficacy in MC38 and B16F10 syngeneic models. In addition, BGB-R046 demonstrated a favorable PK profile in cyno monkeys with clearance and volume of distribution similar to a typical monoclonal antibody. The half-life of BGB-R046 in monkeys was longer than 5 days. Minimum active drug release was observed in plasma with active drug/intact drug ratio lower than 0.2%. BGB-R046 was well tolerated in cyno monkeys.

Conclusions: BGB-R046, an IL-15 pro-drug, demonstrated remarkable in vitro masking capability, significant anti-tumor efficacy in mouse model, favorable PK and safety profile in cyno monkeys. First-in-human study was initiated in 2024Q3 to investigate the BGB-R046 as monotherapy and in combination with tislelizumab (anti-PD-1 therapy) in patients with advanced tumors.