BGB-R046, an IL-15 pro-drug demonstrates robust pharmacodynamic effects and immune activation within tumor microenvironment in a mouse syngeneic model

Yu Jiang,[1,4] Amin Zhang,[2,4] Minjuan Deng,[1,4] Feihong Li,[1] Qinyi Kong,[2] Silu Liu,[1] Xiaoyu Li,[1] Li Luo,[2] Yue Wu,[1] Mengjia Wang,[1] Huixia Hu,[1] Xudong Luan,[1] Xin Chen,[3] Wei Jin,[1,5] Zhirong Shen[1,5]

Authors' Affiliation:[1]BeiGene (Beijing) Co., Ltd., Beijing, China; [2]BeiGene (Shanghai) Biotechnology Co., Ltd., Beijing, China; [3]BeiGene USA, Lnc., Ridgefield Park, NewJersey, USA.
[4]These authors contributed equally to this poster. [5]Correspondence, emails: wei.jin@beigene.com, zhirong.shen@beigene.com

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Background

Interleukin-15 (IL-15) is crucial for the proliferation and survival of NK and memory T cells, and has great potential in cancer immunotherapy. Rapid plasma clearance of conventional IL-15, and therefore insufficient tumor exposure and immune activation, poses a significant limitation in its development as an immuno-oncology therapeutic.

BGB-R046 is developed as an IL-15 pro-drug, which masks free drug release in circulation and is activated in tumors by utilizing tumor enriched proteases to release active IL-15Rα-sushi-IL-15, an IL-15 super-agonist (Luan X, Mei Z, Hu H, *et al.* JITC 2024;12).

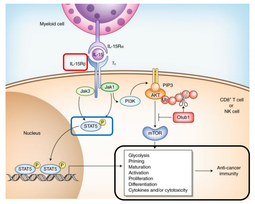
BGB-R046 induced pharmacodynamic effects and immune activation was evaluated in this study, in immune competent mice bearing syngeneic tumor model, to study its pharmacodynamic effects in both circulation and tumor.

Methods

Anti-tumor efficacy was evaluated in the MC38 syngeneic model in IL-15 and IL-15 receptors humanized mice. Active IL-15 released from pro-drug induced downstream signaling events were evaluated in human CD8$^+$T and NK cells. The pharmacokinetics (PK) and pharmacodynamic(PD) biomarkers were evaluated in humanized IL-15/IL-15 receptor mice bearing MC38 syngeneic tumor after BGB-R046 administration.

Results and conclusion

IL-15 induced multiple downstream biological activities can serve as PD biomarkers for BGB-R046



Target: IL-15 receptor β (CD122) — Target engagement and proximal downstream signaling

STAT5 phosphorylation (pSTAT5)

CD8$^+$ T, NK cell proliferation and activation — Distal immune activation as functional markers

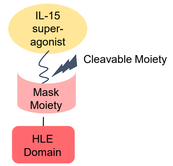
Moynagh, P.N. Nat Immunol 20, 780–782 (2019).

Results: BGB-R046 exhibits protease dependent activation and shows significant anti-tumor efficacy in MC38 syngeneic model. Active pro-IL-15 robustly engages the IL-15 pathway, demonstrated by STAT5 phosphorylation and CD122 downregulation *in vitro*, which are two target engagement PD markers induced by IL-15. Following BGB-R046 administration *in vivo*, minimum active drug release was detected in the circulation while active drug release was more enriched in tumor. Consistently, STAT5 phosphorylation was significantly increased in tumor, while undetectable in circulation on day 7 after BGB-R046 treatment. In addition, surface CD122 level on NK cells was downregulated in tumor while maintained in the circulation, suggesting robust IL-15R target engagement within tumor microenvironment by pro-drug design. Accordingly, BGB-R046 treatment induced significant immune activation in tumor, demonstrated by CD8$^+$ T and NK cell proliferation and activation, consistent with its robust anti-tumor activity in this model.

Conclusion: BGB-R046 is an IL-15 pro-drug with minimum free drug release in the peripheral and induced robust pharmacodynamic effects and immune activation within tumor microenvironment in the MC38 mouse syngeneic model. A clinical study evaluating BGB-R046 as monotherapy and in combination with tislelizumab (anti-PD-1 antibody) in patients with advanced or metastatic tumors is ongoing (NCT06487858).

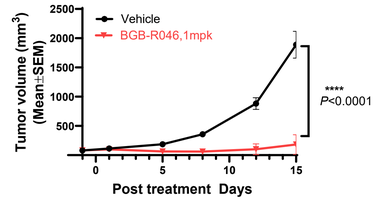
BGB-R046 is an IL-15 pro-drug with minimum free drug release in circulation and enriched IL-15 release in tumor

A. Structural diagram of BGB-R046

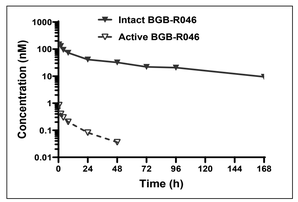


Abbreviations: HLE: half-life extension

B. Significant anti-tumor efficacy by BGB-R046 in MC38 model



C. Minimum free drug release in circulation by BGB-R046 in tumor bearing mice



D. Enriched free drug release in tumor by BGB-R046 in tumor bearing mice

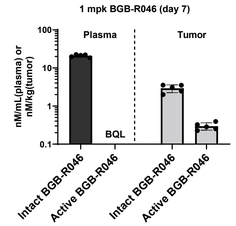
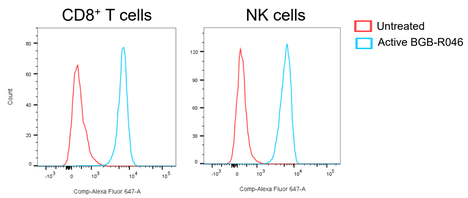


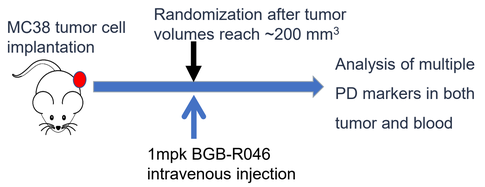
Figure 1. A) BGB-R046 comprises an IL-15 super-agonist, a tumor protease-activatable linker, a masking moiety, and a half-life extension domain. **B)** C57BL/6-hIL2Rβ/hIL2Rγ/hIL-15/hIL-15Rα mice were injected with 0.3 million MC38 cells into the right flank and grouped when tumor volumes reached approximately 80 mm³. Vehicle or 1 mpk BGB-R046 was administered via intravenous injection. **C)** Plasma was collected at the indicated time points to measure intact and active BGB-R046 concentrations using ELISA following 1 mpk BGB-R046 administration. **D)** 1 mpk BGB-R046 was intravenously injected into MC38-bearing mice on day 1. Plasma and tumor tissues were collected on day 7 to detect intact and active BGB-R046 by ELISA (n=5, data shown as mean ± SEM).

STAT5 phosphorylation is significantly induced in the tumor microenvironment

A. Active BGB-R046 induced pSTAT5 in human CD8$^+$T and NK cells *in vitro*



B. Sustained pSTAT5 activation in tumor compared to blood by BGB-R046 in MC38 tumor-bearing mice



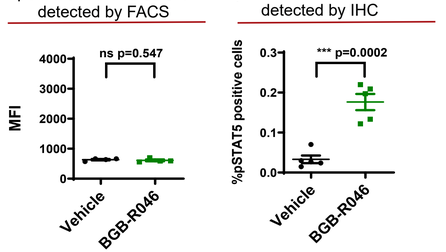
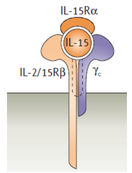


Figure 2. A) Human whole blood was treated with active BGB-R046 *in vitro*, and STAT5 phosphorylation on NK and CD8+ T cells was detected by FACS. **B)** C57BL/6-hIL2Rβ/hIL2Rγ/hIL-15/hIL-15Rα mice were inoculated with MC38 cells and grouped when tumor volumes reached approximately 200 mm³. Following administration of 1 mpk BGB-R046 on day 1, blood and tumor tissues were collected on day 7 for pharmacodynamic studies using FACS or IHC (n=5, data shown as mean ± SEM).

CD122 expression is downregulated by internalization upon binding to IL-15

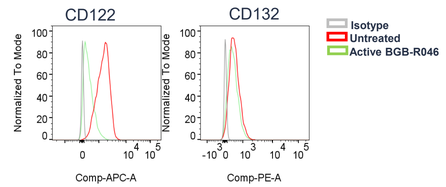
A. Structural diagram of IL-15 receptor complex



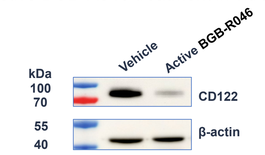
CD122: IL-2/15Rβ
CD132: common gamma chain

Waldmann, T. Nat Rev Immunol 6, 595–601 (2006).

B. Significant reduction of surface CD122, but not CD132 expression by active BGB-R046 *in vitro*



C. Significantly decreased CD122 protein after active BGB-R046 treatment *in vitro*



D. IL-15/IL-15R complex was internalized after active BGB-R046 treatment

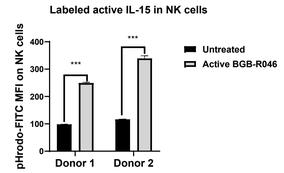


Figure 3. A) Structural diagram of IL-15 receptor complex. **B-C)** Human PBMCs were treated with/without active BGB-R046 *in vitro*, then analyzed for surface expression of CD122/CD132 on NK cells by FACS (B), or CD122 total protein expression by western blot (C). **D)** Human PBMCs were treated with active BGB-R046 labeled with pHrodo™ iFL green dye *in vitro*, and internalized IL-15/IL-15R complex in NK cells was monitored by FACS analysis.

Surface CD122 on NK cells is downregulated in the tumor microenvironment

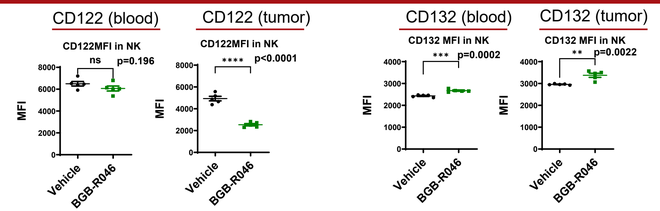


Figure 4. C57BL/6-hIL2Rβ/hIL2Rγ/hIL-15/hIL-15Rα mice were inoculated with MC38 tumor and treated by 1mpk BGB-R046. Blood and tumor tissues were collected on day 7 for CD122 and CD132 analysis by FACS.

BGB-R046 induces robust immune activation in the mouse syngeneic model

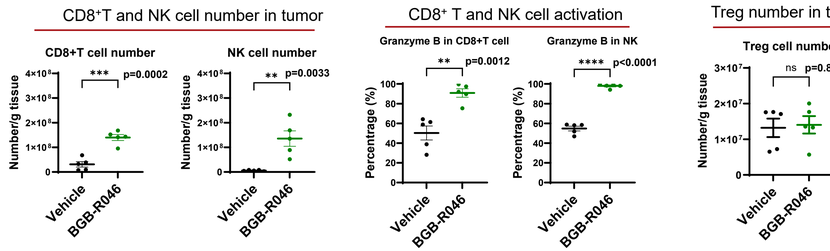


Figure 5. C57BL/6-hIL2Rβ/hIL2Rγ/hIL-15/hIL-15Rα mice were inoculated with MC38 tumor and treated by 1mpk BGB-R046. Tumor infiltrating lymphocytes were isolated and analyzed for immune cell expansion and activation by FACS on day 7 (n=5, data were shown as mean ± SEM).