Abstract #950

Discovery of BGB-R046, an IL-15 Pro-drug that is Conditionally Activated by Proteases in the Tumor Microenvironment for the Treatment of Cancer

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

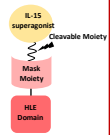
BeiGene (Beijing) Co., Ltd. No. 30 Science Park Rd, Zhong-Guan-Cun Life Science Park, Changping District, Beijing 102206, China. * *Correspondence: xudong.luan@beigene.com*

Background

- IL-15 is a promising cytokine for cancer immunotherapy as it preferentially promotes natural killer and CD8$^+$ T cell expansion.
- However, the clinical use of IL-15 remains limited by systemic toxicities and narrow therapeutic window.
- BGB-R046 is an IL-15 pro-drug (pro-IL-15) under Phase 1 development for the treatment of malignancies.
- BGB-R046 is designed to be activated by tumor enriched proteases to release active IL-15 in tumor microenvironment.

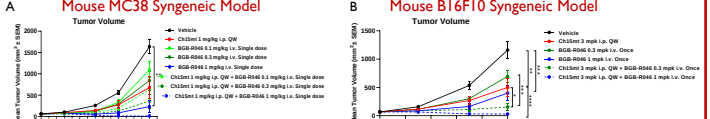
Structural Diagram of BGB-R046

- BGB-R046 consists of IL-15 superagonist, a tumor protease activatable linker, a mask moiety and a half-life extension domain.
- BGB-R046 is inactive in circulation and activated at tumor site by the tumor enriched protease to release IL-15 superagonist.



Abbreviations: HLE: half-life extension.

Strong Anti-tumor Efficacy of BGB-R046 Alone and Combined with PD-1 antibody

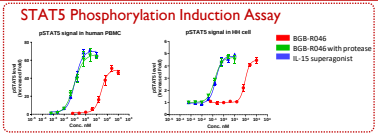


- BGB-R046 alone induced dose-dependent effect on tumor growth inhibition, and statistically significant anti-tumor effect was observed at 1 mg/kg in both MC38 (A) and B16F10 (B) syngeneic models.
- The combination of BGB-R046 at 0.3 and 1 mg/kg with anti-PD-1 antibodies induced dose-dependent effect on tumor growth inhibition compared to single agent treatment in both MC38 (A) and B16F10 (B) syngeneic models.

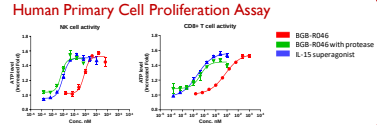
Abbreviations: i.v., intravenously; QW, once weekly; SEM, standard error of the mean. Data are presented as mean ± SEM. Tumor volume was compared on logarithmic scale using Welch ANOVA followed by Dunnett's T3 multiple comparison test (* p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001).

The Protease-activatable Design of BGB-R046 at Cellular Level

STAT5 Phosphorylation Induction Assay



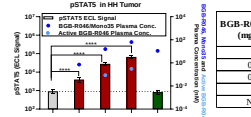
Human Primary Cell Proliferation Assay



In human HH cell line, human PBMC, human NK cell and CD8$^+$ T-cell , BGB-R046 maintained relatively low IL-15 activity, and full IL-15 superagonist activity can be recovered with protease digestion.

Abbreviations: ATP, adenosine triphosphate; PBMC, peripheral blood mononuclear cell; pSTAT5, STAT5 phosphorylation; NK, natural killer.

The Pharmacodynamics Effect of BGB-R046 in Mice Model

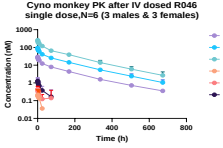


BGB-R046 dose (mg/kg)	Mono-35 dose (mg/kg)	Mean ECL signal of pSTAT5	p-value versus the vehicle group
0	0	888	NA
0.1	NA	3842	< 0.0001
0.3	NA	27234	< 0.0001
1	NA	64832	< 0.0001
NA	1	799	0.9576

** Mono-35 is a pro-IL-15 control with the same format of BGB-R046 but a non-protease-cleavable peptide linker*
NCG mice with HH xenograft model, pSTAT5 as PD readout at 8-hour posttreatment, BGB-R046 was intravenously administered

- BGB-R046 induced dose-dependent and significant increase of tumor pSTAT5 level at dosing range from 0.1 to 1 mg/kg.
- Mono-35, a non-protease-cleavable linker pro-IL-15 control, at 1 mg/kg did not induce pSTAT5 increase, indicating the protease-cleavable linker is critical for the activation of BGB-R046 in tumors.

Pharmacokinetics Profile of BGB-R046



- After intravenous infusion of BGB-R046 in cynomolgus monkeys, a dose-proportional manner and linear PK was observed over the dose range 0.1 to 1 mg/kg.
- The t½ of BGB-R046 was sustained, with the median value ranging from 125 to 135 hours.
- The active/intact drug ratio ($AUC_{0\text{-last}}$) ranged from 0.0132% to 0.134%.

Abbreviations: C_{max}, maximum serum concentrations ranging; $AUC_{0\text{-last}}$, the concentration-time curve from 0 to the last quantifiable concentration; $t_{1/2}$, half-life.

Summary and Conclusions

- *In vitro*, BGB-R046 exhibited relatively low activity, and full IL-15 activity was recovered with protease digestion.
- *In vivo*, BGB-R046 induced dose-dependent and significant increase of tumor pSTAT5 level, while a non-protease-cleavable linker pro-IL-15 control cannot.
- *In vivo*, BGB-R046 alone and combined with PD-1 antibodies showed does-dependent anti-tumor efficacy.
- BGB-R046 demonstrated a favorable PK profile in cyno monkeys similar to a typical monoclonal antibody.
- In sum, the conditional activation of BGB-R046 design demonstrated superior pharmacokinetics, anti-tumor efficacy and safety properties, indicating a remarkably enhanced therapeutic window.
- Phase 1 development of BGB-R046 has started in July 2024 to investigate BGB-R046 alone and in combination with tislelizumab (BGB-A317, an anti-PD-1 antibody) in patients with advanced tumors.