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

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Abstract

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 pose a significant limitation in its development as an immuno-oncology therapeutics. 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(SITC#950). 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.

Method: 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 primary 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: 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 sustained 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.

Conclusions: BGB-R046 is an IL-15 prodrug 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).