BGB-10188, a Highly Selective PI3Kδ Inhibitor with Improved Safety Profile and Superior Anti-Tumor activities in vivo

Xiao Yang[1], Xiaolong Yang[1], Xinxin Cui[1], Dan Su[2], Yue Wu[2], Xuebing Sun[3], Jingyuan Wang[3], Huichen Bai[1], Wei Wei[1], Jing Li[4], Xi Yuan[3], Ye Liu[3], Fan Wang[2], Xuesong Liu[1,3], Xiaomin Song[1]*

Authors' Affiliations: Department of [1]Pharmacology and [2] DMPK and [3] Discovery Biology and [4]Chemistry, BeiGene (Beijing) Co., Ltd., Beijing 102206, P.R.China; **Correspondence: xiaomin.song@beigene.com*

Abstract:

Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes capable of phosphorylating phosphatidylinositol to phosphoinositides, which are important secondary messengers involved in various cell signaling and functions. PI3Kδ is one of four isoforms (PI3Kα, β, δ and γ) of the PI3K class I family. It is restrictively expressed in leukocytes. PI3Kδ is a key signal transduction component for normal and malignant B cells and also important for the homeostasis and function of T-regulatory cells (Treg), making it a promising target for treatment of both hematologic malignancies and solid tumors.

BGB-10188 is a highly selective inhibitor of PI3Kδ, showing no significant inhibition over 376 protein kinases and 17 lipid kinases, and more than three-thousand folds selectivity over PI3Kα, PI3Kβ, and PI3Kγ. BGB-10188 potently inhibited PI3Kδ in biochemical, cellular and human whole blood assays with IC50s ranging from 1.7-16 nM. It also showed a long-lasting and strong target inhibition activity in mouse pharmacodynamics (PD) studies at doses as low as 10mg/kg. The elimination half-life ($t_{1/2}$) of BGB-10188 in plasma was 12.6 hours and 10.4 hours in rats and dogs, respectively.

BGB-10188 showed significant antitumor effects in different types of B cell Lymphoma xenograft models as single agent and enhanced anti-tumor effects in combination with anti-programmed cell death 1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) antibodies in mouse syngeneic models. A dose-dependent inhibitory effect on the percentage of Treg in tumor tissues was also observed after BGB-10188 treatment in vivo.

The liver toxicities of BGB-10188 were evaluated in mice. Significantly improved safety margin was observed for BGB-10188 in comparison with other PI3Kδ inhibitors.

In summary, BGB-10188 is a novel PI3Kδ inhibitor with high selectivity, potency and improved safety profile shown in preclinical studies, which is promising and warrants the testing of the compound in human.