Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes capable of phosphorylating phosphatidylinositol to phosphoinositides, with important secondary messengers involved in various cell signaling and functions. PI3K is one of four isoforms (PI3Kα, β, γ, and δ) 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 PI3Kδ, showing no significant inhibition over 376 protein kinases and 17 lipid kinases, and more than three-thousand folds selectivity over PIK3Cα, PIK3Cδ, and PIK3Cγ. 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 10 mg/kg. The elimination half-life (t1/2) 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 both B cell Lymphoma xenograft and solid tumor models as single agent or in combination with PI3Kδ inhibitors. The liver toxicities of BGB-10188 were evaluated in Balb/c mice, and significantly improved safety profile 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.

**Biochemical and Cellular Potency**

**Table 1: Selectivity and potency of BGB-10188**

<table>
<thead>
<tr>
<th>Assay</th>
<th>BGB-10188 (IC50 nM)</th>
<th>Idelalisib (IC50 nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K δ (Selectivity)</td>
<td>1.7</td>
<td>2.3</td>
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<tr>
<td>PI3K α</td>
<td>4900</td>
<td>430</td>
</tr>
<tr>
<td>PI3K β</td>
<td>5100</td>
<td>360</td>
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<td>PI3K γ</td>
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<tr>
<td>Cell assay IC50 (nM)</td>
<td>Raji (Anti-IGM)</td>
<td>16</td>
</tr>
<tr>
<td>Human blood assay IC50 (nM)</td>
<td>Farage</td>
<td>9.2</td>
</tr>
<tr>
<td>Farage</td>
<td>189</td>
<td></td>
</tr>
</tbody>
</table>

**PD Activity in Mouse**

**Figure 2: PD activity in mouse peripheral blood B cells**

BALB/c mice were treated with 10 and 30 mg/kg of BGB-10188 and euthanized at different time points after dosing as indicated. Whole blood was collected and stimulated by anti-mouse IgD antibody for activating B-cell receptors. The level of pAKT in B cells was measured by flow cytometry.

**Pharmacokinetics Profile**

**Figure 1: PK profiles of BGB-10188 in dog**

Single dose PK in dog (p.o., 10 mg/kg)

- **BGB-10188** showed strong and sustained inhibition on pAKT in B cells in peripheral blood at doses as low as 10 mg/kg in mice.

**Efficacy in B Cell Lymphoma Model**

**Figure 3. Efficacy of BGB-10188 in Farage subcutaneous model**

- Farage tumors (10×10⁶ cells) together with hPBM C (6×10⁶) (B) were implanted subcutaneously in female NCG mice.

**Immune Regulatory Activity in vivo**

**Figure 5. Inhibitory activity of BGB-10188 on Treg**

BALB/c mice with CT26WT tumors were orally treated with BGB-10188 at different doses when tumor volume reached around 80 mm³. The mice were as live as 12 days after drug administration to collect spleen, blood and tumor for immune cell profiling by flow cytometry.

- **BGB-10188 at doses ≥ 3 mg/kg showed inhibitory activity on Treg in blood, spleen and tumor tissues.**

**Liver Toxicity Evaluation**

**Figure 6: ALT and AST level in mice with the treatment of idelalisib and BGB-10188**

BALB/c mice were orally treated with 20 mg/kg of idelalisib or 80, 160 and 300 mg/kg of BGB-10188 twice a day for 20 days.

- **BGB-10188 didn’t induce transaminitis in mice at doses up to 300 mg/kg.**

**Conclusion**

- **BGB-10188 is a potent and highly selective PI3Kδ inhibitor.**
- **BGB-10188 showed long half-life in rat and dog.**
- **BGB-10188 showed dose-dependent anti-tumor activities on B cell malignant tumors in both xenograft and humanized models.**
- **BGB-10188 showed inhibitory activity on Treg in blood, spleen and tumor tissues and increased anti-tumor activity with PD-1 Abs in CT26WT syngenic mouse.**
- **BGB-10188 has improved safety profile regarding to liver toxicities in mice compared to idelalisib.**