BGB-15025, a potent and selective HPK1 inhibitor, is efficacious as a single agent or in combination with PD-1 antibody in multiple tumor models

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Abstract:

Hematopoietic progenitor kinase 1 (HPK1), a hematopoietic cell-restricted serine/threonine protein kinase, has been reported to serve as a critical negative feedback regulator of T lymphocytes by phosphorylating the adaptor protein SLP76 in the TCR complex. The negative feedback role of HPK1 in TCR signaling makes it a promising target for immuno-oncology therapy. It has been recently demonstrated that the kinase activity of HPK1 is essential for its antitumor activity, and HPK1 inhibitors can be potentially combined with immune checkpoint inhibitor therapy (such as PD-1 antibody) for effective cancer treatment.

Here, we report a potent and selective HPK1 inhibitor BGB-15025 which has been identified through in-house high throughput screening and structure-guided drug design. BGB-15025 potently inhibits HPK1 kinase activity in biochemical assay, with a 50% inhibitory concentration (IC50) of 1.04 nM under Km concentration of ATP. Consistently, BGB-15025 can potently reduce SLP76 phosphorylation and increase downstream ERK phosphorylation in a concentration dependent manner in T cells-based assay. As a consequence, BGB-15025 induces TCR activation and IL-2 production in T cells. Owning to the function diversity and high sequence homology among MAP4K family members, it is difficult to develop a selectivity HPK1 inhibitor and spare other MAP4Ks. Based on inhouse profiling, BGB-15025 shows good selectivity profile against other MAP4K family members. Oral administration of BGB-15025 demonstrates dose-dependent pSLP76 inhibition in splenic T cells and induces serum IL-2 in mouse model. In efficacy studies, BGB-15025 demonstrated combination effect with anti-PD-1 antibody in CT26 and EMT-6 syngeneic tumor models. BGB-15025 is currently in phase I clinical trial to treat patients with advanced solid tumor, both as a single agent and in combination with anti PD-1 antibody tislelizumab.