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## 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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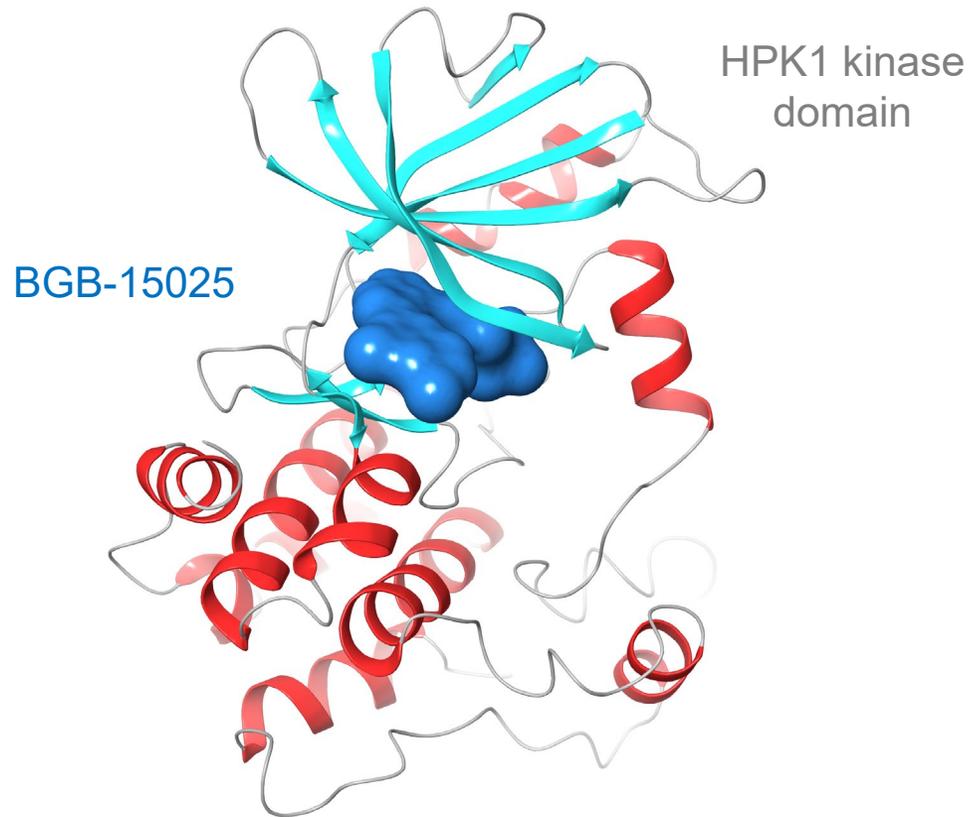
# Contribute equally to this work.

### 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 (IC<sub>50</sub>) 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. Owing 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.

# BGB-15025 is a potent and specific HPK1 kinase inhibitor



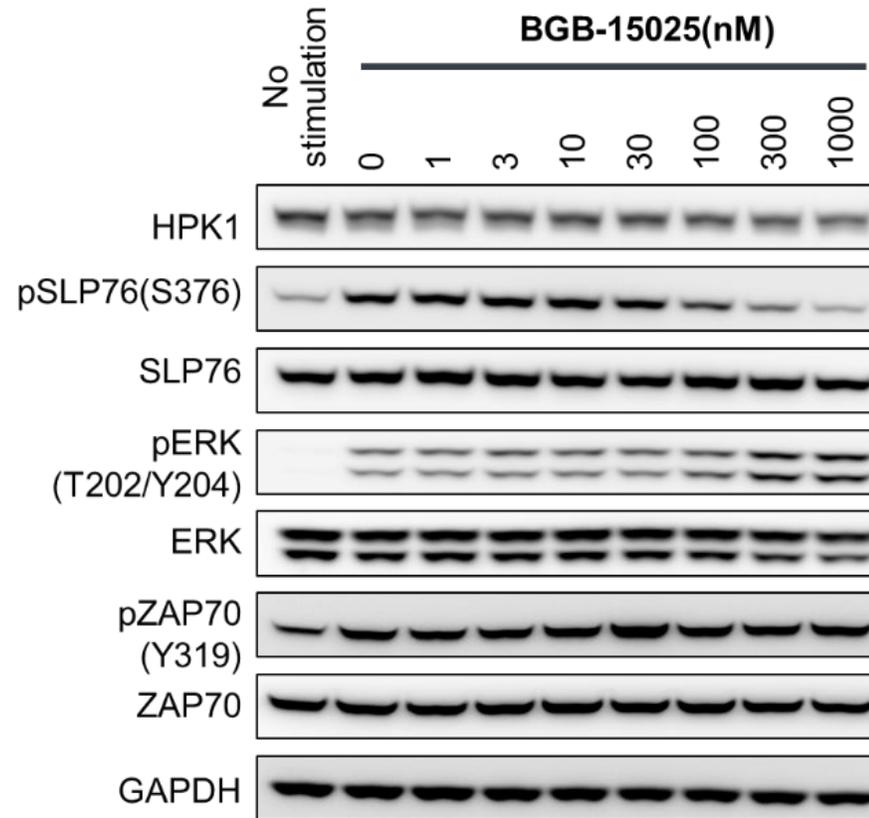
Kinase	IC <sub>50</sub> (nM) of BGB-15025	Assay condition
MAP4K1(HPK1)	1.04	Km ATP
MAP4K1(HPK1)	62	1mM ATP
MAP4K2(GCK)	>10000	1mM ATP
MAP4K3(GLK)	5520	1mM ATP
MAP4K4(HGK)	>10000	1mM ATP
MAP4K5(KHS)	362	1mM ATP
MAP4K6(MINK1)	>10000	1mM ATP

Co-crystal structure of BGB-15025 in complex with HPK1 kinase domain.

# BGB-15025 potently inhibits pSLP76 and activates T cell in vitro

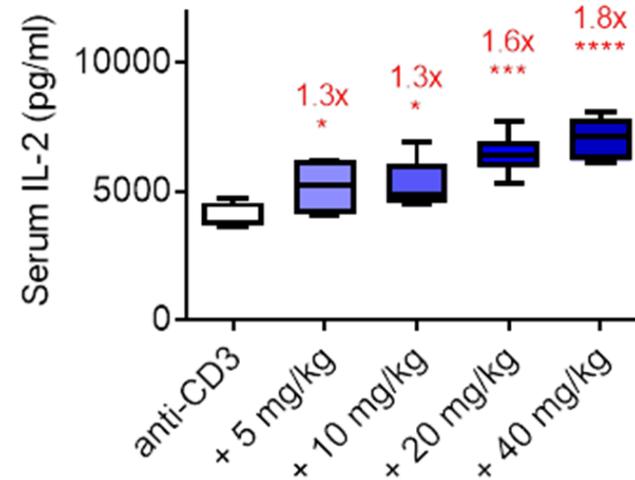
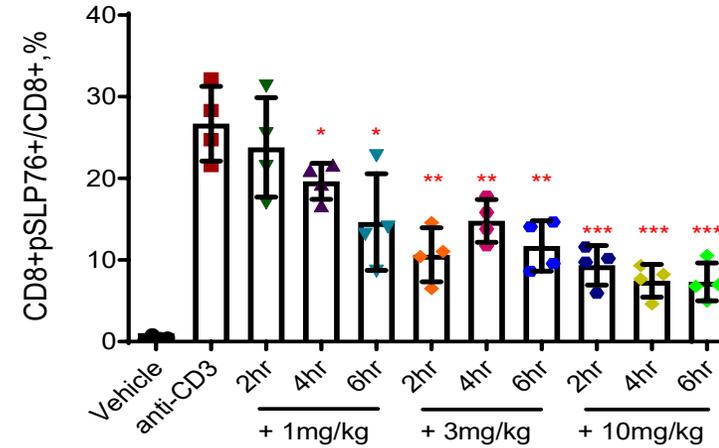
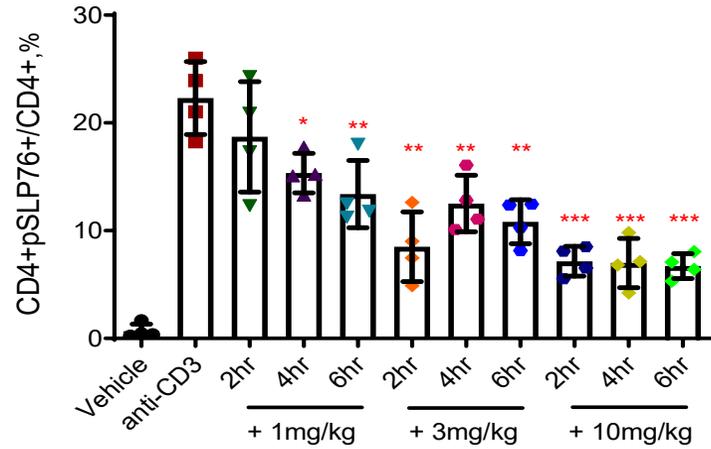
Cells	Stimulation	Molecule Measured	IC <sub>50</sub> /EC <sub>50</sub> (nM) Mean ± Standard Deviation	Fold Increase	n
Jurkat Cells	anti-CD3	pSLP76	150 ± 14	N/A	3
	anti-CD3	IL-2	267 ± 39	5.4 ± 0.6	3
PBMC	anti-CD3 plus anti-CD28	IL-2	261 ± 64	4.3 ± 1.7	3

# BGB-15025 has a good selectivity to HPK1 over other proximal components of the TCR complex

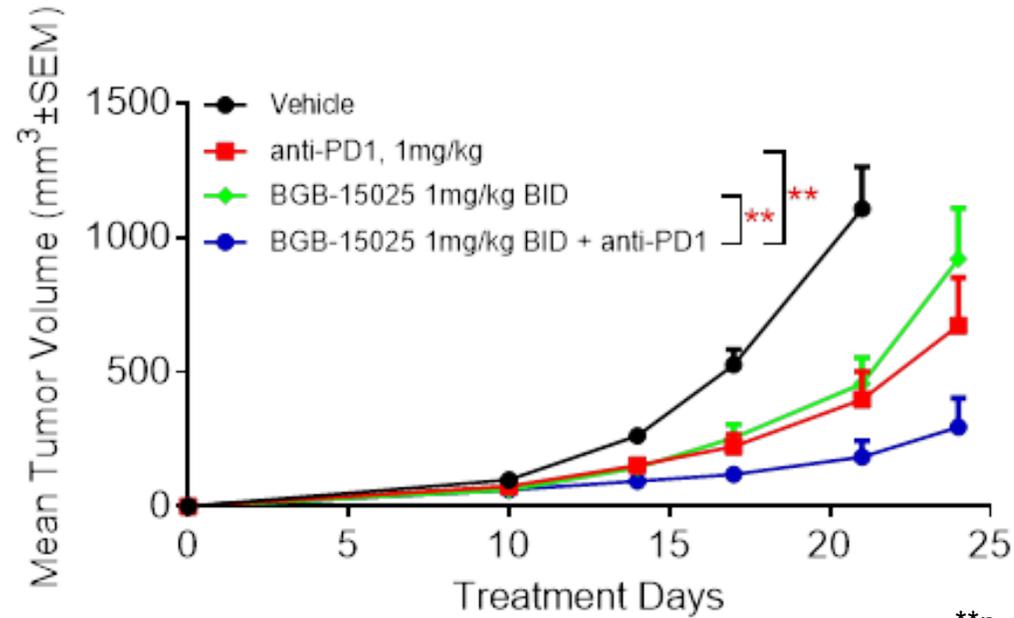


BGB-15025 inhibited SLP76 phosphorylation and increased ERK phosphorylation but not affect ZAP70 phosphorylation up to 1  $\mu$ M.

# Dose-dependent in vivo pSLP76 inhibition and IL2 production induced by BGB-15025



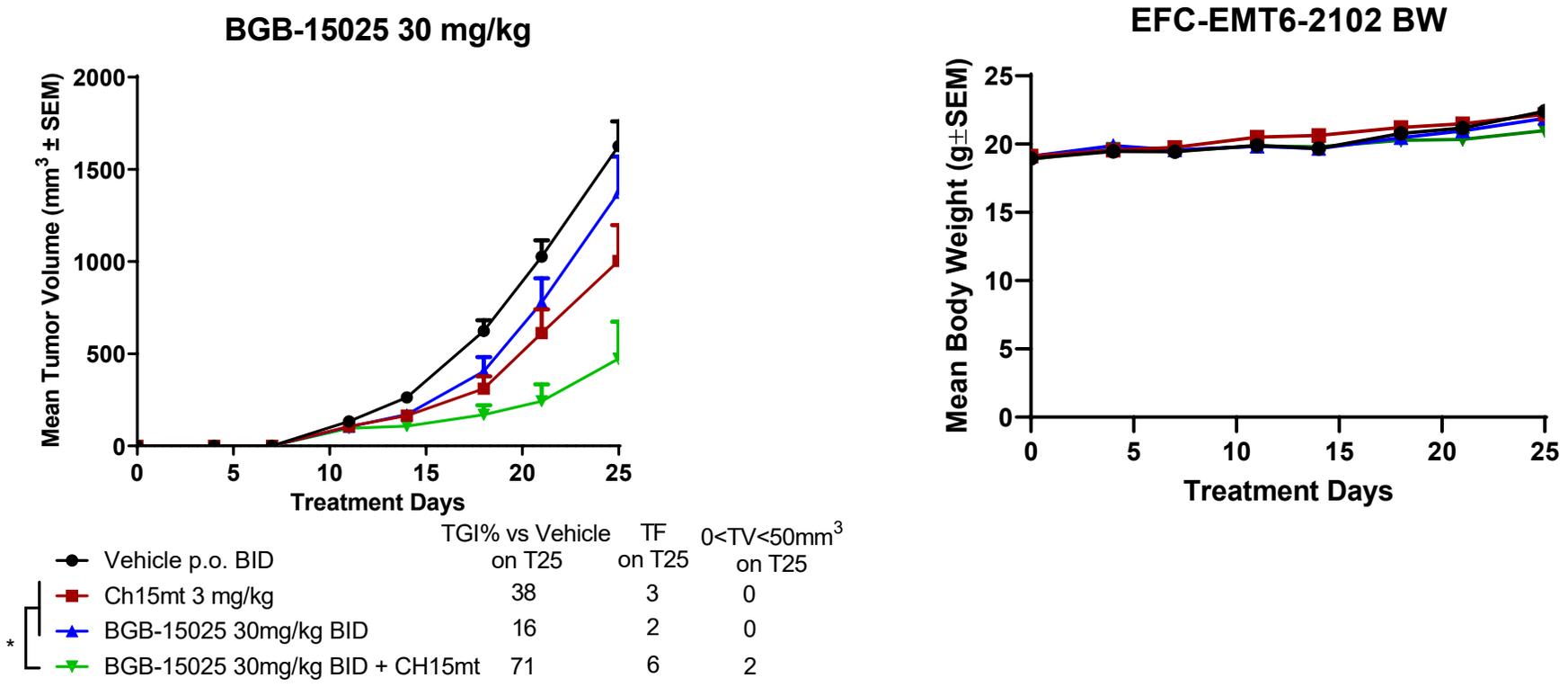
# BGB-15025 shows anti-tumor efficacy in CT-26WT model as single agent and combo with anti-PD1



\*\*p < 0.01 calculated by EOHSA criterion

Efficacy of the combination of BGB-15025 and anti-PD1 in syngeneic CT26WT model in BALB/c mice.

# BGB-15025 and anti-PD1 shows significant combo anti-tumor efficacy in EMT-6 model



\* p < 0.05 calculated by EOHSA criterion



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