Background
Hematopoietic progenitor kinase 1 (HPK1, MAP4K1), is a negative regulator of T and B cell receptor signaling.\(^1\) A strong anti-tumor immunogenic response and tumor rejection was observed in mice with HPK1 gene knocked out.\(^1\)\(^2\)\(^3\) Treatment of HPK1 kinase dead mice with immune check-point blockers (ICBs) demonstrated enhanced tumor growth inhibition.\(^3\) Hence, HPK1 is an attractive therapeutic strategy for immuno-oncology based treatment in cancers. In comparison to our previous HPK1 small molecule inhibitor, PCC,\(^4\) we present here a differentiated novel HPK1 inhibitor, PCC-1 with good anti-T cell kinases selectivity and stronger anti-tumor efficacy in CT26 tumor model. In addition, using the syngeneic model of MC38 expressing human PD-L1, we present for the first time, the combination efficacy of a HPK1 inhibitor with the clinical ICB, Atezolizumab.

Methods
Intuitive medicinal chemistry complemented by structure-based drug design was used to identify & develop potent inhibitors of HPK1 with optimal kinase selectivity, PK and in vivo efficacy profile. The SAR efforts were guided by biochemical assays, functional read-outs and primary human in vitro T-cell activation assays. In vivo target engagement and pharmacodynamic data was generated using CT26 and MC38-hPD-L1 tumor models.

Results
PCC-1 has sub-nanomolar HPK1 inhibition potency and strong target engagement resulting in pSLP76 inhibition, enhanced anti-tumor cytokine production of IL-2 and/or IFN-gamma in Jurkat cells, human PBMCs and human whole blood. PCC-1 also demonstrated nanomolar potency in inducing a complete reversal of PGE2 or adenosine mediated immunosuppression. Oral dosing of PCC-1 as a single agent, induced strong tumor growth inhibition (TGI) in the syngeneic model of CT26 and MC38-hPD-L1 tumor models. Combination of PCC-1 with anti-CTLA4 in CT26 tumor model induced significantly greater TGI than anti-CTLA4 alone. Moreover, as a first, the combination of PCC-1 with clinical ICB, Atezolizumab in MC38-hPD-L1 induced enhanced rejection of tumors. These results strongly suggest PCC-1 as a promising candidate for HPK1 inhibition and as a combination partner with ICBs in clinic.

Conclusions
PCC-1 is a novel, orally active HPK1 inhibitor that demonstrates excellent stand-alone efficacy and enhances current immunotherapy efficacy. Further evaluation of PCC-1 is ongoing to advance towards clinic.

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Trial Registration
N/A

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