848 NOVEL SMALL MOLECULE HPK1 INHIBITOR PCC-1 INDUCES STRONG ANTI-TUMOR ACTIVITY

¹Sanjib Das, ¹Sravan Mandadi*, ¹Jagmohan Saini, ¹Sachin Chaudhari, ¹Ameya Deshpande, ¹Murugan Chinnappattu, ¹Malini Bajpai, ¹Priyanka Pangre, ¹Varada Potdar, ¹Megha Marathe, ¹Pooja Sawant, ¹Atul Akarte, ²Chandrasekhar Misra, ¹Subhadip Das, ¹Anuj Singh, ¹Avratanu Das, ¹Pandurang Lambade, ¹Chaitanya Tirumalasetty, ¹Raju Patole, ¹Nilanjana Biswas, ¹Vikas Karande, ¹Heta Shah, ¹Dayanidhi Behera, ¹Nagaraj Gowda, ¹Pravin Iyer. ¹Glenmark Pharmaceuticals Limited, Navi Mumbai, India; ²Glenmark Pharmaceuticals, Navi Mumbai, India

Background Hematopoietic progenitor kinase 1 (HPK1, MAP4K1), is a negative regulator of T and B cell receptor signaling.^{1 2 3} A strong anti-tumor immunogenic response and tumor rejection was observed in mice with HPK1 gene knocked out.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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Ethics Approval The studies involving animals have obtained ethics approval from Institutional Animal Ethics Committee (IAEC), The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India, GRC/IAEC/472/2020-1. Participants of the studies have given informed consent before taking part.

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