PERK INHIBITOR HC-5404 DEMONSTRATES IMMUNE-ACTIVATION AND ANTI-TUMOR EFFICACY IN COMBINATION WITH ANTI-PD1 IMMUNE CHECKPOINT INHIBITOR ANTIBODY

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Background Protein kinase R-like endoplasmic reticulum kinase (PERK) is part of the unfolded protein response that facilitates cellular adaptation to ER stress. PERK is activated in cancer cells by accumulation of misfolded proteins in the ER, enabling adaptation and survival. PERK signaling has also recently been implicated in maintaining immunosuppressive functions of myeloid-derived suppressor cells (MDSCs) through inhibition of a type 1 interferon response and macrophages through metabolic and epigenetic modification. We are developing HC-5404, a highly selective and potent first-in-class, first-in-human PERK inhibitor that is currently in a phase 1 trial for solid tumors (NCT04834778). HC-5404 has demonstrated single agent and combinatorial efficacy in multiple solid tumor xenograft models. In this study, we sought to investigate the immunomodulatory effects of HC-5404 by evaluating efficacy and correlative immune effects of HC-5404 combined with an anti-murine-PD-1 immune checkpoint inhibitor (ICI) antibody.

Methods C57BL/6 mice were subcutaneously inoculated with syngeneic MB49 bladder cancer cells, and treatment started on day 8 post cell inoculation. A group of animals (n=10/group) received either vehicle, HC-5404 (PO, BID), anti-PD-1 antibody RMP1-14 (IP, every 3 days), or the combination of both. At various timepoints, flow cytometry was performed on blood or single cell suspensions from tumors or lymph nodes (n=6) of treated mice. MDSCs derived from human cord blood or mouse bone marrow were co-cultured with purified T-cells in the presence of HC-5404 in vitro, and proliferation was evaluated.

Results HC-5404 treatment alone showed only a modest anti-tumor effect (32% TGI), the addition of HC-5404 to aPD-1 provided combination antitumor benefits (75% TGI) and significantly improved the effects of aPD-1 alone (53% TGI). HC-5404 + aPD-1 efficacy was correlated with increased expression of type 1 interferon receptor (IFNAR1) and increased surface calreticulin on tumor cells. Additionally, IFNAR1 was also significantly increased on PMN-MDSCs and tumor-associated macrophages (TAM). TAMs also showed increased PD-L1 with combination treatment. Additionally, combination treatment increased the frequency of CD8 T-cells in the tumor along with increased expression of activation marker CD69 on T-cells in the tumor draining lymph node. Notably, the effect of HC-5404 on IFNAR1 was also detected on monocytes in peripheral blood, demonstrating surface expression of IFNAR1 as a potential biomarker for HC-5404 activity. MDSCs also showed a reduced inhibition of T-cells in the presence of HC-5404 in vitro.

Conclusions Collectively, these data demonstrate the efficacious and immuno-stimulatory effects of HC-5404 coadministered with anti-PD1 mAb and outline its potential application in ICI-treated cancers.

REFERENCES

Ethics Approval All in vivo experimental procedures were done in accordance with the NIH Guide for Care and Use of Animals and were approved by the Institutional Animal Care and Use Committee of University of Minnesota. IACUC protocol 2009A38458