A HIGHLY-SELECTIVE HPK1 INHIBITOR ENHANCES T CELL RECEPTOR SIGNALING AND T CELL ACTIVATION POTENTIAL, INCREASING ANTIGEN RECOGNITION AND EFFICACY OF PD-1 THERAPY

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Background Recognition of neoplastically transformed cells as foreign is the cornerstone to effective immune surveillance of cancer. Neo-antigens generated by mutations that accumulate in tumors are the basis of immune rejection, and higher levels correlate with responses to PD1 blockade. Unfortunately, most patients have insufficient tumor mutation burden (TMB) to benefit from current immunotherapies, and/or their mutations do not produce sufficiently robust antigens that can break central immune tolerance. Enhancing the ability of a patient’s immune system to respond to existing TMB is paramount to overcoming primary resistance to PD1 blockade.

The HPK1 kinase is critically involved in T cell receptor (TCR) signaling, initiating a negative-feedback loop that raises the threshold of stimulus required for T cell responses. Genetic ablation of HPK1 kinase activity has been shown to increase T cell responsiveness to antigen stimulus and improve activity of PD-1 blockade in preclinical models, making HPK1 an attractive target for immunotherapy. However, the high homology of the HPK1 active site with other kinases, including kinases necessary for productive TCR signaling, results in off target liabilities that can limit small-molecule inhibitors from unlocking the full-potential of HPK1 inhibition.

Methods Through structure-based drug design and optimizing for enhanced T cell proliferation, we identified the highly-selective HPK1 inhibitor PF-07265028. Kinome selectivity of PF-07265028 was verified through biochemical profiling and in-cell chemical probes.

Results Treatment of primary human T cells from multiple human donors with PF-07265028 shows a dose-dependent inhibition of SLP76 phosphorylation (pSLP76) while increasing proliferation following suboptimal TCR stimulation. By virtue of HPK1 selectivity, PF-07265028 maintains the ability to enhance immune responses at concentrations well-above that required for 90% inhibition of pSLP76. Inhibition of HPK1 with PF-07265028 increased both CD8 and CD4 cytokine recall responses to MHC-presented peptides, and enabled resistance to immunosuppressive metabolites (PGE2 and adenosine) that can otherwise activate HPK1 through their receptors. Combination of PF-07265028 with an anti-PD-1 antibody in co-cultures of human T cells and cancer cells led to increased tumor cell killing through synergistic enhancements of T cell activation and cytokine production. PF-07265028 displayed immunostimulatory activity in non-human primates including markers of T cell activation.

Conclusions Based on its ability to enhance multiple axes of T cell activation, PF-07265028 has the potential to improve anti-tumor responses in patients resistant to immunotherapy. Therefore, a phase one study has thus been initiated to evaluate the safety and efficacy of PF-07265028 alone and in combination with PD-1 blockade in patients with advanced solid tumors.