A Highly Selective and Potent HPK1 Inhibitor Induces Robust Tumor Growth Inhibition as a Single Agent and in Combination with anti-PD1 in Multiple Syngeneic Tumor Models

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BACKGROUND
HPK1, a member of the MAP4K family of protein serine/threonine kinases, is involved in negatively regulating signal transduction cascades in cells of hematopoietic origin. This negative-feedback role in cells of hematopoietic origin, make it a compelling drug target for enhancing anti-tumor immunity.

METHODS & RESULTS
EMT6, a highly potent HPK1 inhibitor that has been developed using a classic SBDD approach. Statistically significant inhibition, including a number of complete CRs, was observed across the broader kinome was identified using a single agent activity was observed across multiple mouse syngeneic models, including 7CRs in the NMBS-2, a highly potent HPK1 inhibitor that has been developed using a classic SBDD approach. Statistically significant single agent activity was observed across multiple mouse syngeneic models, including 7CRs in the EMT6 model. In combination with anti-PD1, NMBS-2 restored cytokine secretion from exhausted human T cells, induced robust tumor growth inhibition in the CT-26 model, and resulted in a highly effective immune memory response.

CONCLUSIONS AND FUTURE STEPS
We show here that a potent, highly selective small molecule HPK1 inhibitor demonstrates significant tumor growth inhibition, including a number of complete responses (as defined by no measurable tumor present) as a single agent and in combination with anti-PD1 in multiple mouse syngeneic tumor models. Furthermore, the combination of HPK1 inhibition and anti-PD1 resulted in complete rejection of CT-26 tumor rechallenge in previously treated animals, suggesting the establishment of a robust and durable state of immune memory. Further evaluation of these selective inhibitors in additional in vivo studies will continue to build upon our mechanistic understanding of HPK1 inhibition as a novel immunomodulatory approach for anti-tumor immunity.