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 of HPK1 downstream of lymphocyte activation and function, combined with its restricted expression in cells of hematopoietic origin, make it a compelling drug target for enhancing anti-tumor immunity.

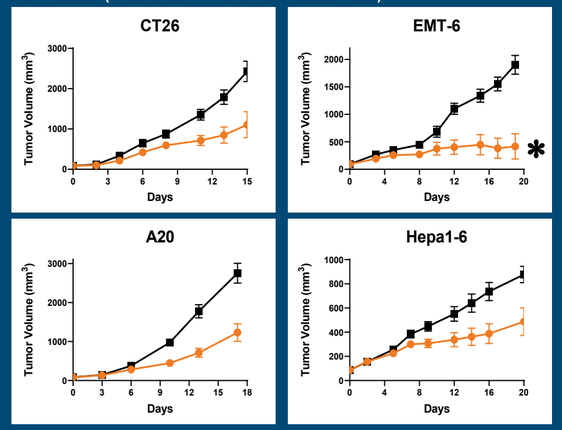
METHODS & RESULTS

NMBS-2, a highly potent HPK1 inhibitor that has exquisite selectivity within the MAP4K family and across the broader kinome was identified 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.

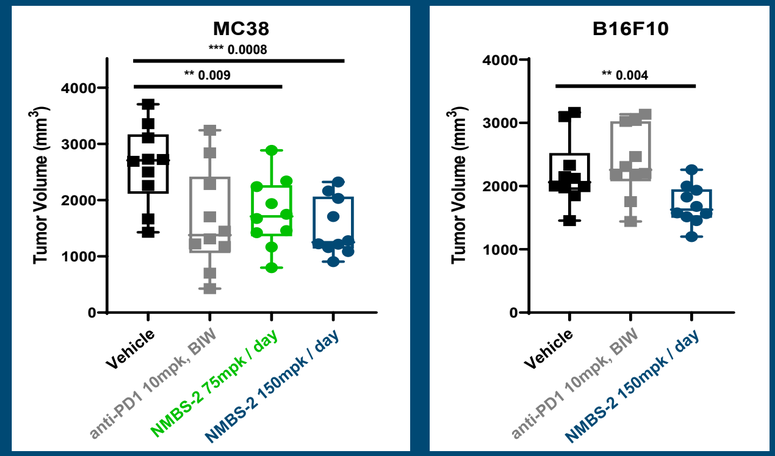
SINGLE AGENT ACTIVITY

NMBS-2 induces robust single agent tumor growth inhibition in 4 of 12 syngeneic models (MuScreen™ Crown Biosciences)

Observed Response	Cell Line	Cancer Indication	TGI P-value NMBS-2 vs Vehicle	Percent TGI NMBS-2 vs Vehicle
Robust	CT26	Colon	0.005	54%
	A20	Lymphoma	0.0003	55%
	EMT-6	Breast	<0.0001	78%
	Hepa1-6	Liver	0.008	44%
Partial (n.s.)	H22	Liver	0.09	32%
	MC38	Colon	0.19	32%
	LL/2	Lung	0.14	13%
	Renca	Kidney	0.06	23%
None	Pan02	Pancreatic	0.93	-1.7%
	RM-1	Prostate	0.84	2%
	B16F10	Melanoma	0.78	2%
	B16BL6	Melanoma	0.18	-13%

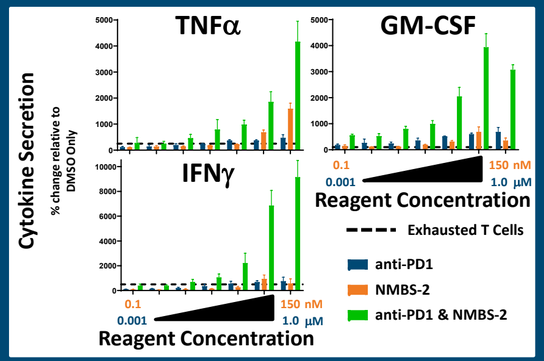


In parallel studies, statistically significant tumor growth inhibition was observed for both the MC38 and B16F10 syngeneic models with NMBS-2

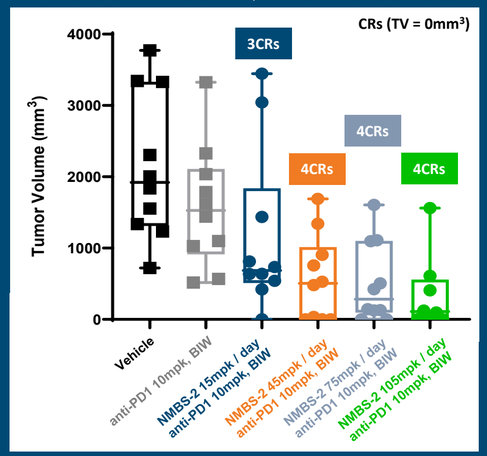


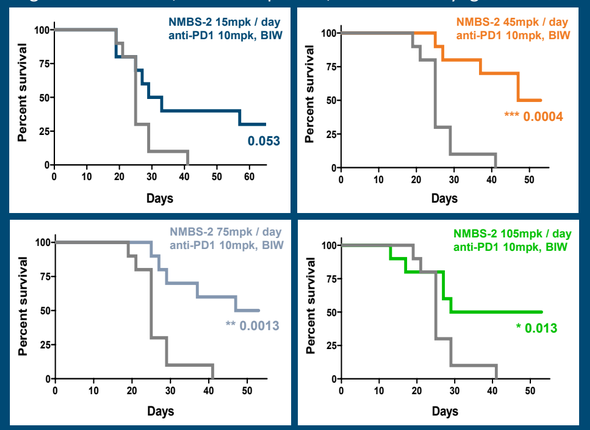
COMBINATION ACTIVITY

HPK1 inhibition synergizes with anti-PD1 to restore cytokine secretion from exhausted human T cells in a mixed lymphocyte reaction



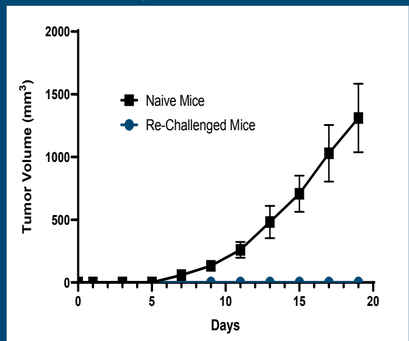
In combination with anti-PD1, NMBS-2 induces robust tumor growth inhibition, with multiple CRs, in the CT-26 syngeneic model





Tumor growth is completely inhibited in CT-26 tumor re-challenged animals

Dosing was discontinued for 7 days in all animals achieving a CR in the CT-26 model (previous figure). Animals were then re-challenged with CT-26 tumor cells and tumor growth monitored for 20 days.



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 re-challenge 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.

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