449 CYCLIC DISRUPTION OF THE MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) PATHWAY BY THE DUAL MEK INHIBITOR, IMM-6-415, ENHANCES PD1 AND CTLA4 CHECKPOINT BLOCKADE IN RAS MUTANT TUMORS

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Background KRAS is the most frequently altered RAS gene (~85%) and is often mutated in pancreatic ductal adenocarcinoma (PDAC; 95%), non-small cell lung cancer (NSCLC; 40%) and colorectal cancer (CRC; 45%). KRAS-G12C inhibitors (sotorasib/adagrasib) have demonstrated single-agent activity in all three tumor types. However, acquired resistance and limited biomarker positive patients (e.g., only 1-3% of PDAC and CRC) limit broader access and overall response to G12C inhibitors, prompting evaluation of combination partners including immune therapies. In contrast to G12C-mutant focused KRAS inhibitors, MEK inhibitors may broaden the potential for immune therapy in RAS-mutant tumors but have largely proven ineffective in this setting.

Methods IMM-6-415 is a novel, third-generation dual MEK inhibitor that reduces both pMEK and pERK in RAS-mutant tumor models at sub-100 nM potencies. IMM-6-415 drug-like properties have been evaluated across a series of preclinical *in vitro* and *in vivo* models focusing on activity in those with mutant RAS. Cell-based 2D and 3D biochemical and pharmacologic assays were performed across multiple models, and several *in vivo* studies have been completed, including: (1.) A549 (KRAS-G12S NSCLC) xenograft model, (2.) Colon-26 (KRAS-G12D CRC) syngeneic model, (3.) CT-26 (KRAS-G12D) syngeneic model. The CT-26 *in vivo* study evaluated both single-agent IMM-6-415 and combinations with PD1 or CTLA4 checkpoint inhibitors.

Results IMM-6-415 reduced pERK and pMEK across all RAS mutant models tested. Humanized 3D tumor models revealed a promising sensitivity profile for IMM-6-415 in RAS-mutant CRC and PDAC. The maximum tolerated dose (MTD) of IMM-6-415 was 175 to 180 mg/kg BID PO from the Colon-26 (96.4% TGI) and A549 (93.9% TGI) studies, yet the optimal MEKio combination dose/schedule was 120 mg/kg BID PO in the CT-26 study. At 28 days treatment, 33% (4/12) mice remained on study in either the (10 mg/kg BIW IP) anti-PD1 or anti-CTLA4 alone treated groups, whereas 58% (7/12) mice remained in the IMM-6-415 treatment arm at 120 mg/kg BID PO. However, 92% (11/12) and 83% (10/12) mice remained in the IMM-6-415 plus anti-PD1 or anti-CTLA4 combination at the same doses, respectively.

Conclusions We demonstrate that IMM-6-415 displays single-agent activity in multiple RAS-mutant models, has a 0.3h half-life, is well tolerated in mice, and when combined at sub-MTD levels with either PD1 or CTLA4 checkpoint inhibitors, significantly improved responses in the CT-26 model (p-value < 0.05). Our data suggest that moderated, cyclic inhibition of the MAPK pathway in RAS mutant tumors is active and may enhance therapeutic activity of immune checkpoint inhibitors.

Ethics Approval The protocol and any amendment(s) or procedures involving the care and use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of CrownBio prior to execution. During the study, the care and use of animals was conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

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