Cyclic disruption of the mitogen-activated protein kinase (MAPK) pathway by the Dual MEK inhibitor, IMM-6-415, enhances PD-1 and CTLA-4 checkpoint blockade in RAS mutant tumors

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Introduction

KRAS is the most frequently altered RAS gene (~45%) 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 (cotaximab/dalutigib) have demonstrated single-agent activity in all these tumor types. However, acquired resistance and limited biomarker positive patients (e.g., only 13% 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-mutated focused KRAS inhibitors, MEK inhibitors can broaden the potential for immune therapy in RAS-mutant tumors, but they have been largely ineffective in this setting as monotherapy. Here, we demonstrate that the short-lived Dual MEK inhibitor, IMM-6-415, is active across multiple MAPK-driven tumor models both as a single agent and in combination with checkpoint inhibitors (CP).

Methods

IMM-6-415 is a novel, third-generation Dual MEK inhibitor that reduces both pMEK and pERK in RAS- and RAF-mutant tumor models at sub-100 nM potencies. IMM-6-415 was evaluated in a series of preclinical in vitro and in vivo models enriched for activation mutations that increase MAPK pathway signaling. Cell-based 2D biochemical and 3D pharmacologic assays were performed along with multiple in vivo studies in RAS mutant and wildtype models: (1) Colon 26, a KRASG12D CRC syngeneic model; (2) A549, a KRASG12S NSCLC xenograft model; (3) CT-26, a KRASG12D syngeneic model and (4) MC38, a RAS wild-type syngeneic model. CT-26 (8BILic) and MC38 (C57BL/6) in vivo studies evaluated single-agent IMM-6-415, PD-1 and CTLA-4 versus IMM-6-415 + CPI combinations.

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 RAF- and RAS-mutant models. The maximum tolerated dose (MTD) for BID dosing of IMM-6-415 was 175 mg/kg BID PO based on Colon 26 (86.4% TGI) and A549 (89.9% TGI) studies, yet enhanced MEKi + CPI combinations were identified at only 120 mg/kg BID PO IMM-6-415. At 28 days treatment, 35% (4/12) CT-26 mice remained in study on the 10 mg/kg BIW IP anti-PD-1 or anti-CTLA-4 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-PD-1 or anti-CTLA-4 combination at the same doses.

Figure 1. IMM-6-415: a Dual-MEK Inhibitor in RAS and RAF Mutant Tumors

Key Mutations & 3D-TGA Response

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<th>pERK to Total-ERK Ratio</th>
<th>pMEK to Total-MEK Ratio</th>
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<td>(100 nM Drug)</td>
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Figure 2. IMM-6-415 Displays a Short Plasma & Tumor PK Half Life In Vivo

Table 1. Differentiating Characteristics of 1st, 2nd, 3rd Generation MEK Inhibitors

Table: Differences in 1st, 2nd, 3rd Generation MEK Inhibitors

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Figure 3. Drug Pharmacology and Maximum Effective Dose (MED) in Mice

Figure 4. MEKI, a-PD-1, a-CTLA-4 Alone and Combinations in CT-26 / MC38

Conclusions

Elevated MAPK pathway signaling can promote deleterious effects on antitumor immunity, which has prompted multiple MEKI plus CPI combination trials. However, MEKi class effect toxidromes have limited clinical utility of MEKi combinations. Instead of chronic MAPK pathway ablation, IMM-6-415 was designed to drive short bursts of Crx driven inhibition of MEK. IMM-6-415 displayed activity across multiple RAS- and RAF-mutant tumor models, and when combined with PD-1 or CTLA-4 checkpoint inhibitors at well-tolerated, sub-MED dose levels, significant survival benefit was observed (p-values: <0.05 to <0.0001; CT-26). These data suggest that moderated, cyclic inhibition of MEK in combination with CPIs may improve survival times versus monotherapy in MAPK-activated tumors. Antitumor responses with IMM-6-415 + CPIs in an immune compromised CT-26 model at the same doses, combinations and schedules were not observed, suggesting that moderated, cyclic disruption of the MAPK pathway can enhance CPI-dependent adaptive antitumor immunity and improve overall MEKi combination tolerability.

References