The next-generation farnesyltransferase inhibitor KO-2806 constrains compensatory signaling reactivation to deepen responses to KRASG12D inhibition

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Abstract # 34971

CONCLUSIONS
• The combination of KO-2806 and MRTX1133 has superior antitumor activity compared to MRTX1133 monotherapy in KRASG12D-mutant CRC and PDAC xenograft models while remaining well-tolerated.
• KO-2806 performs as well or better than cetuximab when paired with MRTX1133 in a CRC model, making it a viable combination partner.
• Mechanistically, KO-2806 blocks the compensatory reactivation of mTOR signaling that follows KRASG12D inhibition, resulting in tumor cell cycle arrest and apoptosis.

BACKGROUND
• The landmark approval of KRASG12C inhibitors has fueled the design and development of small molecules targeting other oncogenic KRAS mutants, including the most prevalent, KRASG12D.
• MRTX1133 is the first KRASG12D-selective inhibitor to reach the clinic. Preclinical MRTX1133 data and early clinical results from KRASG12D inhibitor trials suggest that responses to KRASG12D inhibition will vary, in part due to incomplete and/or transient inhibition of MAPK and mTOR signaling.
• We have previously demonstrated that farnesyltransferase inhibitors (FTIs) can prevent adaptive properties of tumor cells, poised to enter a first-in-human clinical trial.
• We hypothesized that KO-2806 would enhance the antitumor activity of MRTX1133 by blocking feedback reactivation of mitogenic and survival signaling; we evaluate the therapeutic potential of this combination here.

OBJECTIVES
• Evaluate the in vitro tolerability and efficacy of KO-2806 and MRTX1133 in KRASG12D-mutant xenograft models
• Assess impact of combination on MAPK and mTOR signaling in vitro and in vivo to delineate mechanism of action

RESULTS
KO-2806 blocks reactivation of mTOR following KRASG12D inhibition and induces apoptosis in vitro

Figure 2. Combined KO-2806 and MRTX1133 durably inhibits MAPK/mTOR signaling and induces apoptosis in the PDAC cell line CR1245. Immunoblots of the indicated MAPK/PI3K pathway components and phenotype markers in the KRASG12D-mutant PDAC cell line CR1245 treated with 100 nM MRTX1133 for 0, 4, 24, or 48 hours in the presence or absence of KO-2806. Shift in RHEB mobility is indicative of unfarnesylated state.

KO-2806 and cetuximab have comparable antitumor activity when combined with MRTX1133 in CRC model

Figure 4. Both KO-2806 and cetuximab deepen response of colorectal CDX model to MRTX1133. A. Growth of GP2D CRC tumors treated with vehicle, KO-2806, MRTX1133 (20 mg/kg IP, BID), or the combination for 28 days. Best average response of GP2D tumors from per mRECIST. B. Best average response of GP2D tumors from per mRECIST.

Figure 5. The KO-2806 MRTX1133 combination potently inhibits mTOR, arrests cell cycle in G1D2D-mutant CRC tumors. GP2D CDX tumors were treated with vehicle, KO-2806, MRTX1133 (20 mg/kg IP, BID), or the combination for 28 days. Tumors were harvested and snap frozen for immunoblot analysis 2 hours post-treatment on day 28. Combination treatment resulted in stronger inhibition of mTOR (as indicated by lower levels of S6 and 4EBP1 phosphorylation) and cell cycle arrest (decreased Rb phosphorylation) compared with MRTX1133 monotherapy-treated tumors.

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Figure 6. Mechanistic rationale for combining a farnesyltransferase inhibitor with an inhibitor of KRASG12D. KRAS inhibition with a small molecule inhibitor such as MRTX1133 transiently blocks MAPK-mTOR signaling, relieving negative feedback on upstream pathway components such as receptor tyrosine kinases. Induction of these pathway activators leads to reactivation of mTOR signaling through PI3K or WT RAS isoforms. By inhibiting the obligately-farnesylated mTOR activator RHEB, farnesyltransferase inhibitors such as KO-2806 impede reactivation of mTOR, resulting in durable mTOR inhibition, cell cycle arrest, and cell death.