ABSTRACT #390

The next-generation farnesyl transferase inhibitor KO-2806 sensitizes colorectal cancers to pan-RAS inhibition

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BACKGROUND

- Emerging clinical and preclinical mechanistic data have demonstrated that KRAS-mutant colorectal cancers (CRCs) are less responsive to mutant-selective KRAS inhibitors than lung cancers.
- This discrepancy has been attributed to higher basal receptor tyrosine kinase (RTK) activity and frequent oncogene co-mutation in CRC.
- Pan-RAS inhibitors, such as RMC-6236, are also under clinical investigation in CRC, but it is unknown whether their efficacy will be limited by similar lineage-specific factors, given that pan-RAS inhibition should prevent signaling reactivation through wildtype RAS.
- We have previously shown that farnesyl transferase inhibitors (FTIs) sensitize tumors to targeted agents such as PI3Kα and mutant-selective KRAS inhibitors by blocking RHEB's activation of mTOR.
- We hypothesized that RTK-mediated reactivation of PI3K-AKT-mTOR signaling would remain a liability of pan-RAS inhibitors in CRC, and that the FTI KO-2806 would enhance the activity of RMC-6236 in RAS-inhibitor naïve and pretreated settings by blunting this adaptive response.

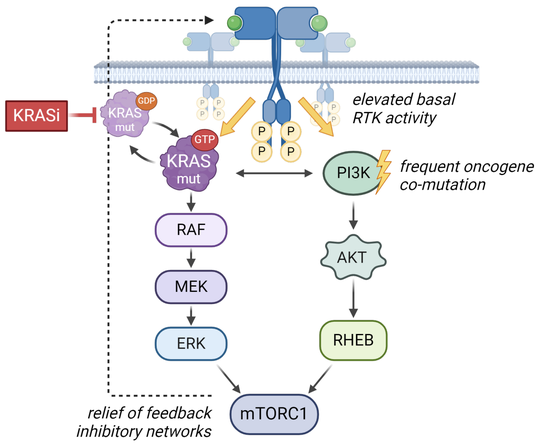

Figure 1. Factors limiting efficacy of mutant-selective KRAS inhibitors in colorectal cancer.

RESULTS

Reactivation of mTOR signaling remains a liability with pan-RAS inhibitors and is targetable by KO-2806.

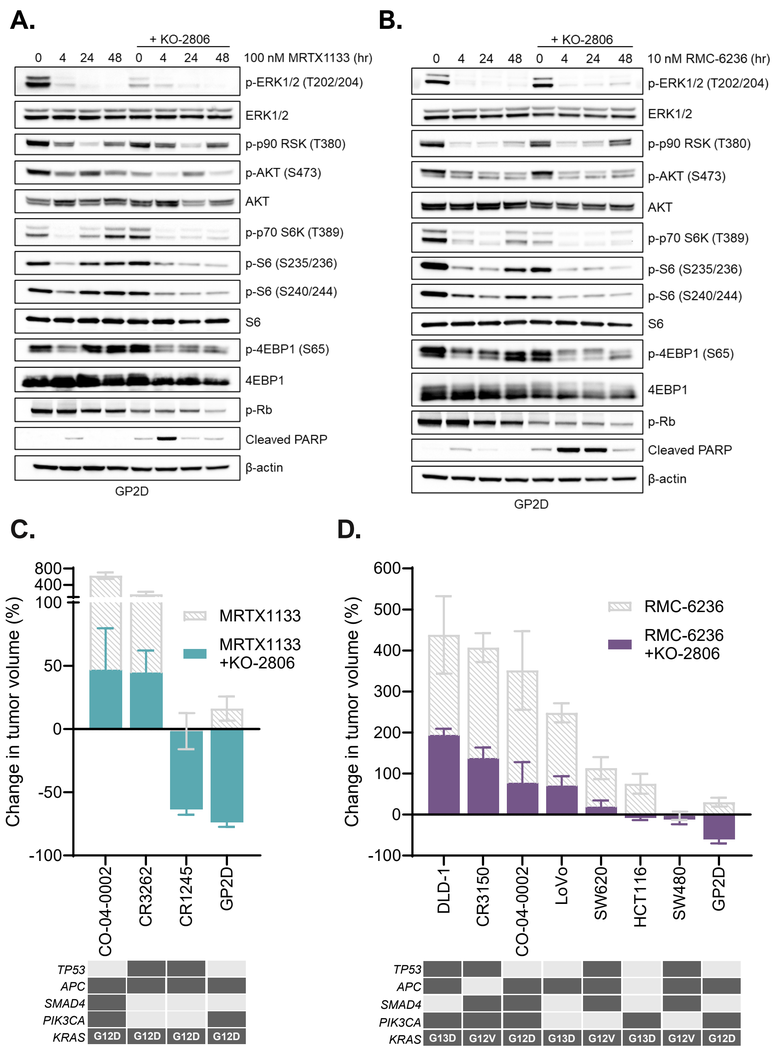

Figure 2. Farnesyl transferase inhibition blocks reactivation of mTOR signaling and enhances tumor growth inhibition by KRAS^{G12D}-selective and pan-RAS inhibitors in preclinical CRC models. A and **B.** Immunoblots of the indicated signaling proteins in GP2D CRC cells exposed to (**A**) 100 nM MRTX1133 or (**B**) 10 nM RMC-6236 for 0, 4, 24, or 48 hours in the presence or absence KO-2806. **C** and **D**. Tumor efficacy waterfall plots of KRAS-mutant CRC xenograft models treated with 10-30 mg/kg MRTX1133 IP BID (**C**), or 10-25 mg/kg RMC-6236 PO QD (**D**) as monotherapy (gray bars) or in combination with KO-2806 (colored bars). Each bar represents the mean percent change in tumor volume at treatment day 28 relative to baseline (day 0), ± SEM, n = 8 animals per group. Oncoplots illustrating the mutational status of key driver genes as well as the KRAS mutation codon in each model are shown below each waterfall plot. Mutations are indicated by dark gray shading.

Enhanced tumor growth inhibition by pan-RAS/ KO-2806 combination correlates with deeper mTOR inhibition in vivo.

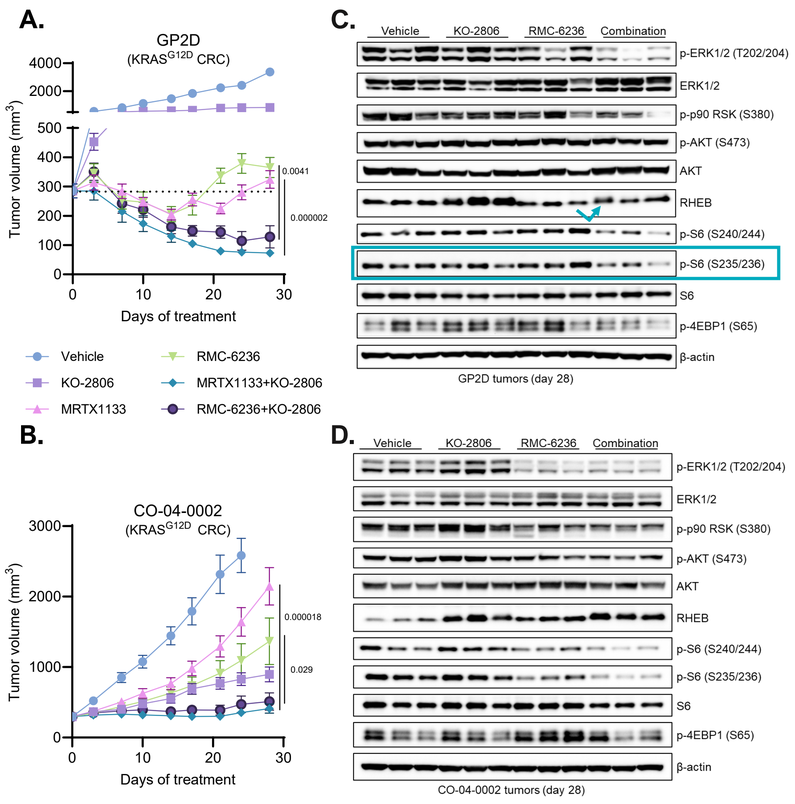

Figure 3. KO-2806 deepens antitumor and mTOR-inhibitory effects of RAS inhibitors in CRC. A. Growth of GP2D xenograft tumors treated with vehicle, KO-2806, MRTX1133 (10 mg/kg IP BID), RMC-6236 (25 mg/kg PO QD), or KO-2806-RAS inhibitor doublets. **B.** Growth of CO-04-0002 tumors treated with vehicle, KO-2806, MRTX1133 (20 mg/kg), RMC-6236 (25 mg/kg), or combinations. Data are means ± SEM; n =8 mice per group. Statistical significance determined by unpaired Student's t-test, p-values as indicated on plot. **C** and **D**. Immunoblots of indicated signaling proteins in GP2D (**C**) or CO-04-0002 (**D**) tumors treated as indicated in **A** and **B** for 28 days. Shift in RHEB mobility is indicative of unfarnesylated state.

Pan-RAS inhibition induces the activity of multiple HER-family receptors in vivo, mechanistically supporting combination with KO-2806 over cetuximab

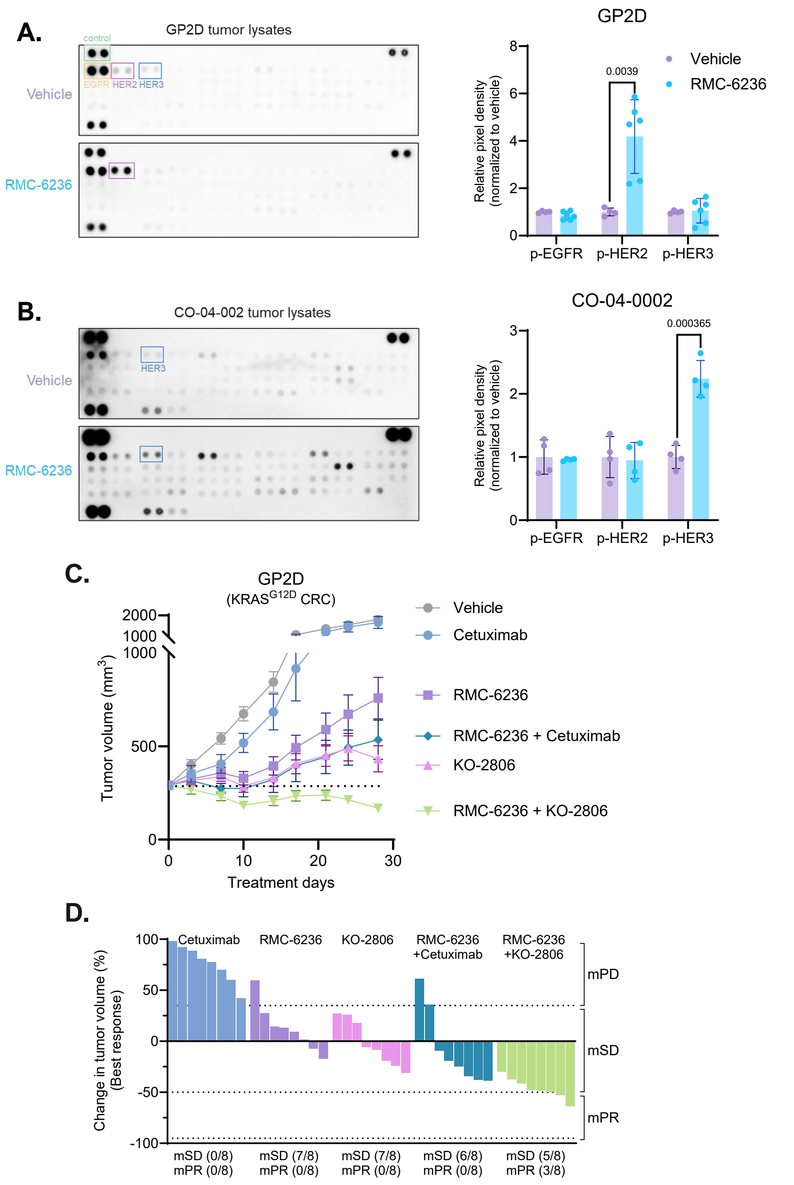

Figure 4. KO-2806 outperforms Cetuximab as a pan-RAS combination partner in KRAS-mutant CRC models due to activation of multiple RTKs. A and **B**. GP2D (**A**) and CO-04-0002 (**B**) tumors treated for 28 days with vehicle or RMC-6236 were lysed and subjected to phospho-RTK array analysis. Images representative of 2-3 tumors per group. Signal intensity was quantified by measuring phospho-spot pixel density relative to control spots and normalized to vehicle control tumors. Statistical significance determined by unpaired Student's t-test. **C**. Growth of GP2D xenograft tumors treated with vehicle, Cetuximab (0.25 mg/dose IP Q3D), RMC-6236 (10 mg/kg PO QD), KO-2806, or combinations. **D**. Waterfall plot of best responses (% change in tumor volume from baseline) of each animal on treatment in (**C**). Response calls (below) were made using mRECIST criteria.

KO-2806 re-sensitizes relapsing CRC xenograft tumors to RAS inhibition

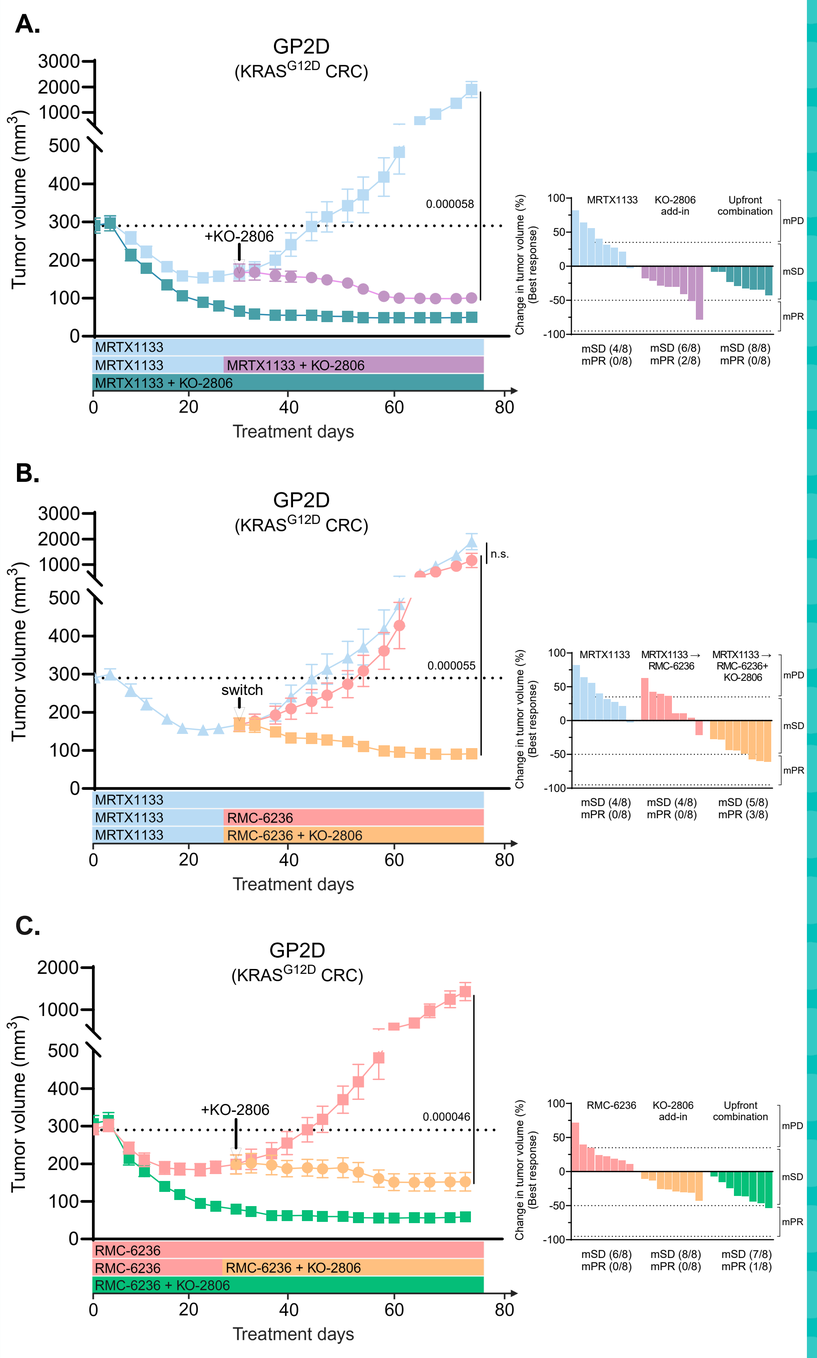

Figure 5. Addition of KO-2806 re-sensitizes progressing CRC xenograft tumors to mutant-selective or pan-RAS inhibition. A-C. Growth of GP2D xenograft tumors treated with KO-2806, 25 mg/kg RMC-6236, 10 mg/kg MRTX1133, or FTI/RASi combinations as indicated on the timelines below tumor volume plots. Tumor progression on single agent RAS inhibitors was seen by 28 days, at which time KO-2806 was added and/or RAS inhibitor was switched. Each point is the mean ± SEM of 8 mice. Waterfall plots (right) are best responses after day 28, with response calls made according to mRECIST.

CONCLUSIONS

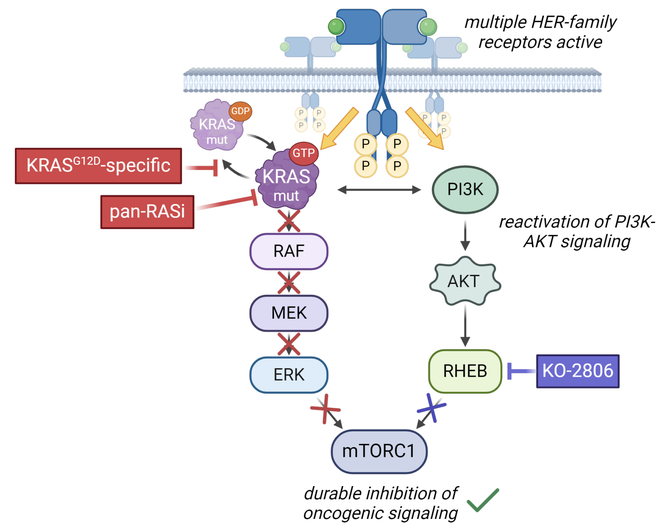

Figure 6. The farnesyl transferase inhibitor KO-2806 controls persistent mTOR signaling to synergize with RAS inhibition in colorectal cancer.

- As previously demonstrated for mutant-selective KRAS inhibitors, reactivation of mTOR signaling remains a liability for pan-RAS inhibitors that is targetable by KO-2806, enhancing antitumor effects.
- Basal EGFR activity is high in CRCs, and pan-RAS inhibitor treatment induces additional HER-family members. As such, the combination of RMC-6236 and Cetuximab is ineffective at controlling growth of xenograft tumors, while the KO-2806/RMC-6236 combination leads to durable signaling inhibition and tumor regression.
- Addition of KO-2806 re-sensitizes progressing xenograft tumors to mutant-selective or pan-RAS inhibitors.
- Given its ability to control persistent mTOR signaling mediated by the elevated RTK activity in CRC, KO-2806 holds promise as a partner agent to augment the therapeutic potential of mutant-selective and pan-RAS inhibitors regardless of prior RAS-inhibitor exposure.