Farnesyl transferase inhibition restores RAS inhibitor sensitivity in tumors exhibiting innate or adaptive resistance

Ali Smith
Kura Oncology, Inc., San Diego, CA

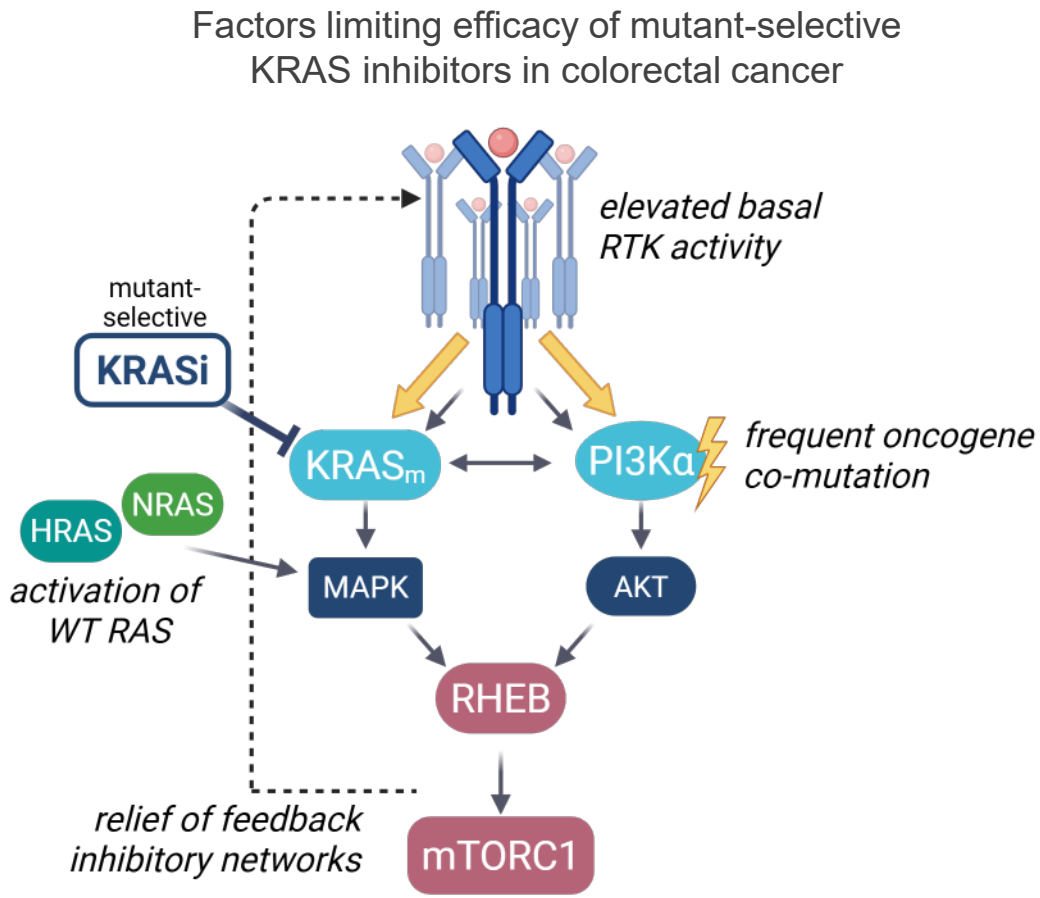
RAS-Targeted Drug Development Summit
16-18 September 2025

Disclosure Information

Employee and stockholder of Kura Oncology, Inc.

Potential utility of pan-RAS inhibitors in *KRAS*-mutant CRC

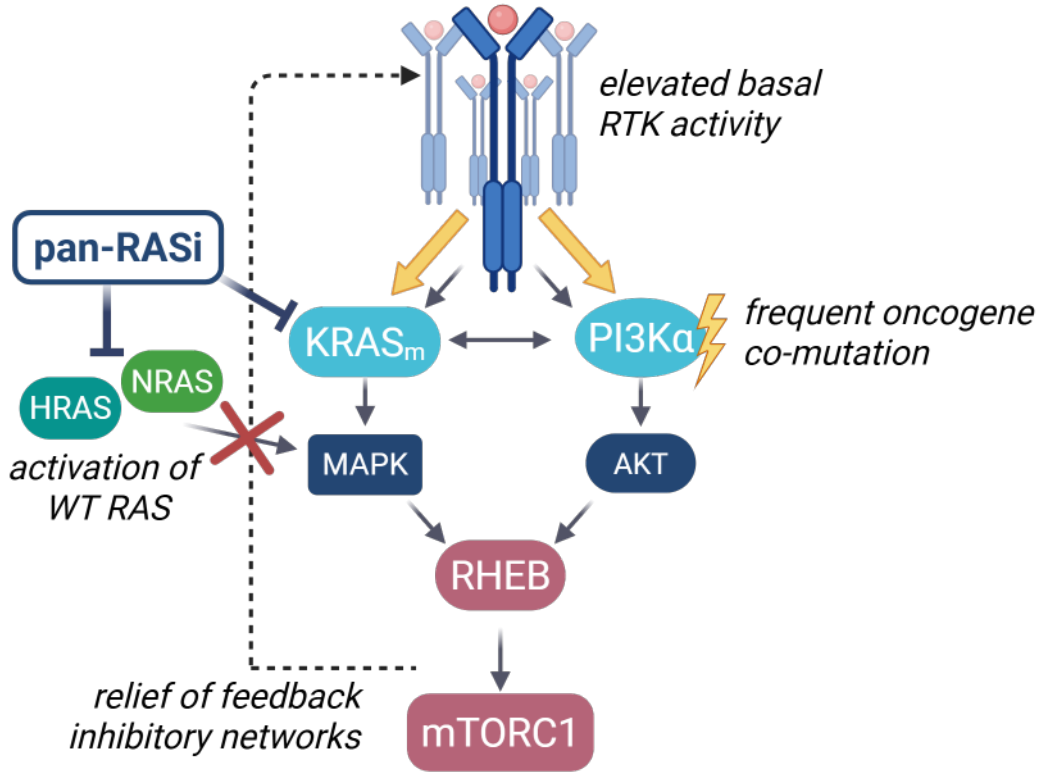
- Approved G12C-selective KRAS inhibitors only target ~3% of colorectal cancers (CRCs)
- CRCs are less responsive to mutant-selective KRAS inhibitors than lung cancers due to higher basal receptor tyrosine kinase (RTK) activity[1,2] and frequent oncogene co-mutation → combination strategies required



1 Ryan, MB, et al. *Clin Cancer Res* 2020 26(7):1633-1643
2 Ryan MB, et al. *Cell Reports* 2022 39(12):110993
3 Jiang J, et al. *Cancer Disc* 2024 14(6):994-1017

Potential utility of pan-RAS inhibitors in *KRAS*-mutant CRC

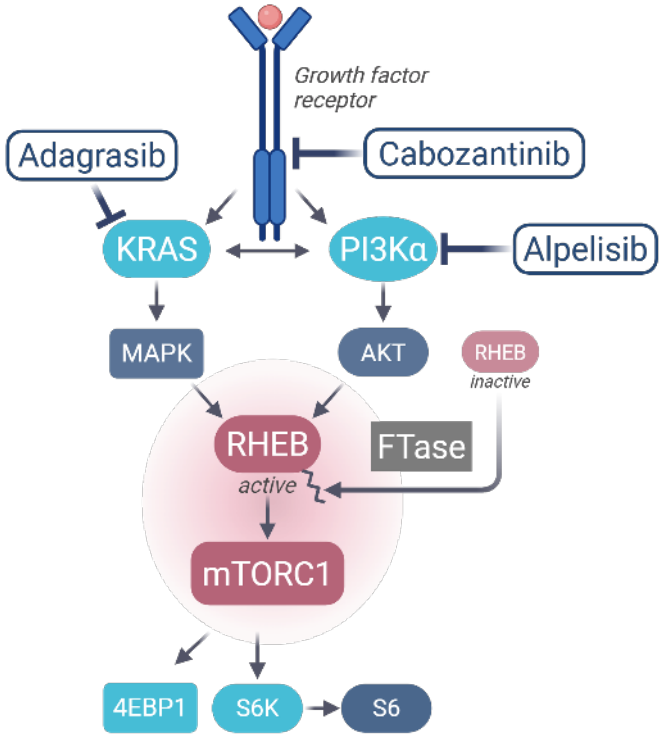
- Approved G12C-selective KRAS inhibitors only target ~3% of colorectal cancers (CRCs)
- CRCs are less responsive to mutant-selective KRAS inhibitors than lung cancers due to higher basal receptor tyrosine kinase (RTK) activity[1,2] and frequent oncogene co-mutation → combination strategies required
- Pan-RAS inhibitors like daraxonrasib (RMC-6236) may be more effective monotherapies given they should prevent signaling reactivation through wildtype (WT) RAS[3]



1 Ryan, MB, et al. *Clin Cancer Res* 2020 26(7):1633-1643
2 Ryan MB, et al. *Cell Reports* 2022 39(12):110993
3 Jiang J, et al. *Cancer Disc* 2024 14(6):994-1017

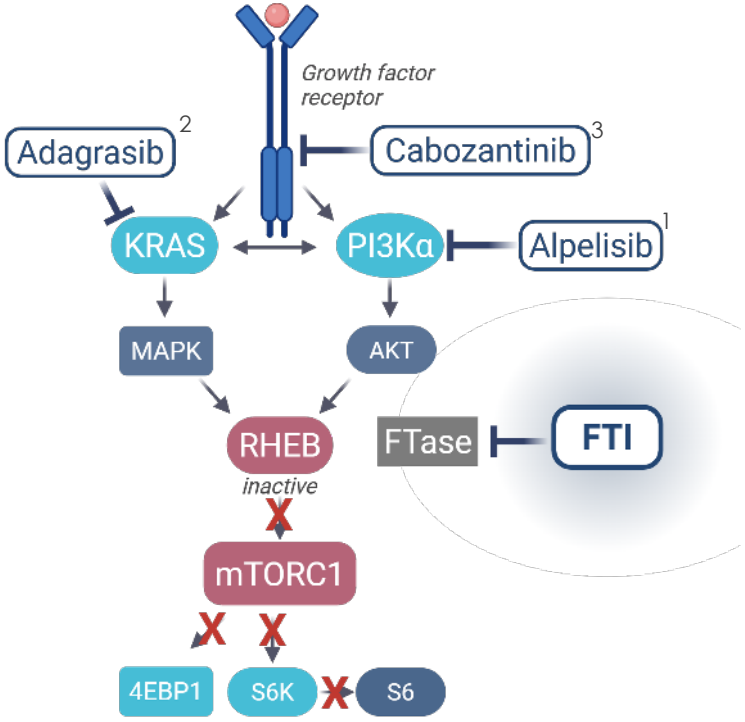
Farnesyl transferase inhibitors (FTIs) sensitize tumors to targeted therapies via RHEB-mTORC1

Single-agent targeted therapy



Residual mTORC1 activity drives tumor cell growth and therapy escape

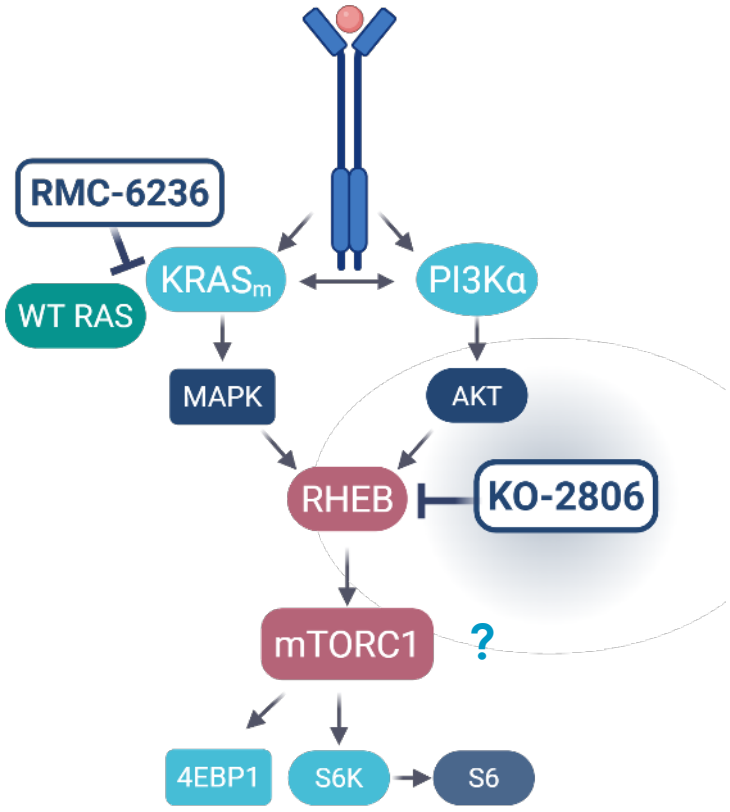
FTI-based combinations



Deep and durable mTORC1 inhibition

1 Smith, AE. et al. *Cancer Res* 2023. 83(19):3252-63.
2 Patel, HV. Smith, AE. et al. *bioRxiv* 2024.12.20.629824.
3 Gasendo, JG. et al. *Cancer Res* 2025. 85(8_Supplement_1):6370

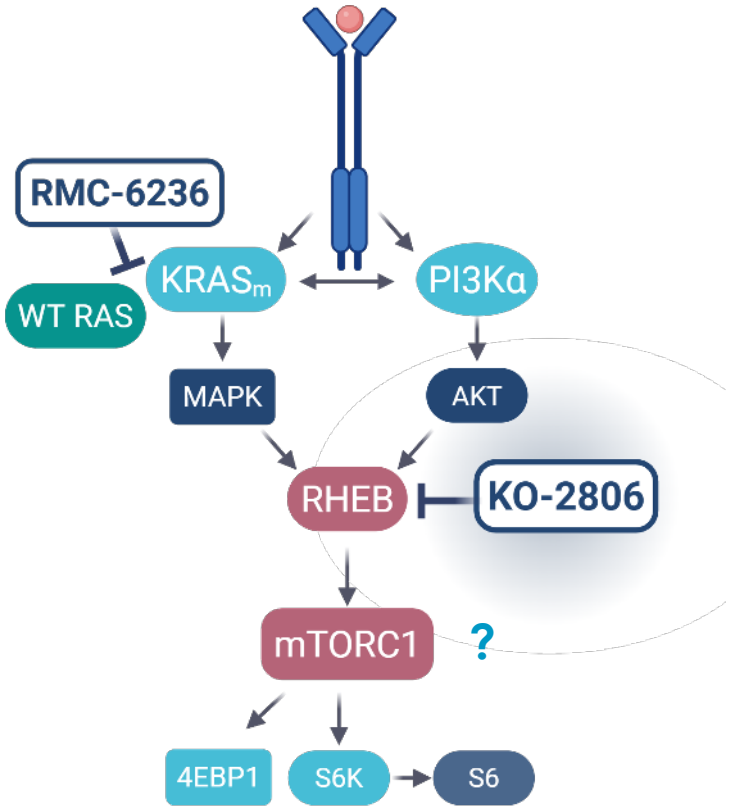
Mechanistic rationale for combined FTI and pan-RASi in CRC

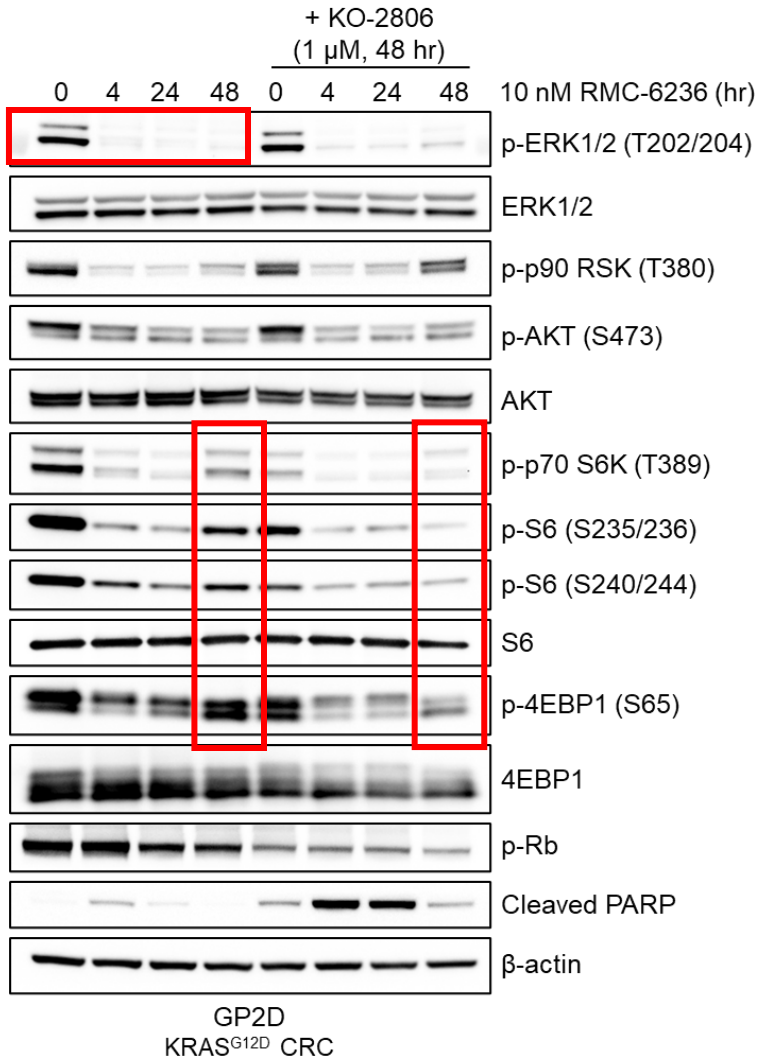


Does RTK-mediated (re)activation of PI3K-AKT-mTORC1 still occur in the presence of pan-RASi?

Can the next-generation FTI KO-2806 enhance the activity of pan-RAS inhibition in CRC?

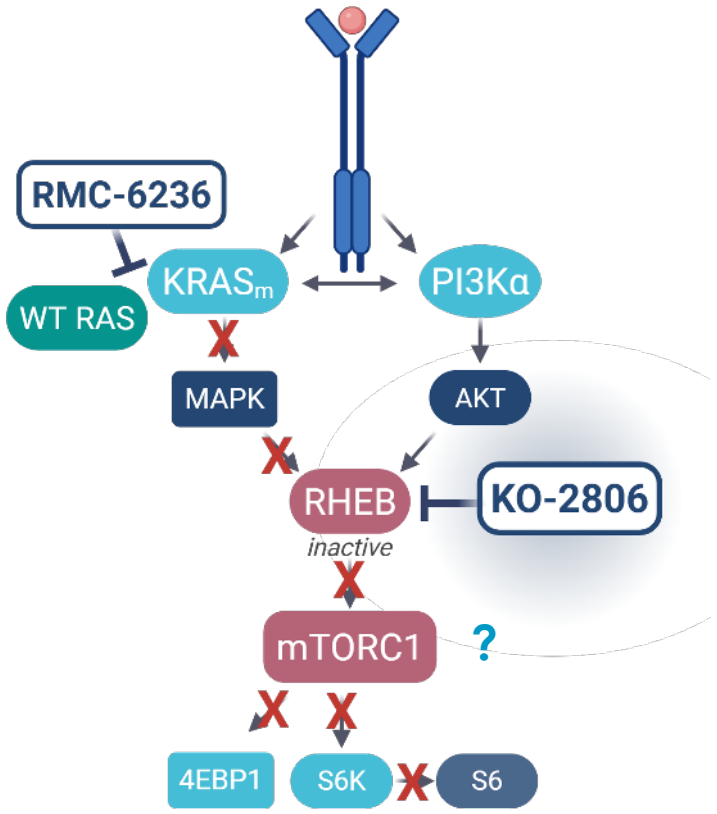
Persistent mTORC1 signaling remains a liability with pan-RAS inhibition and is targetable with the FTI KO-2806

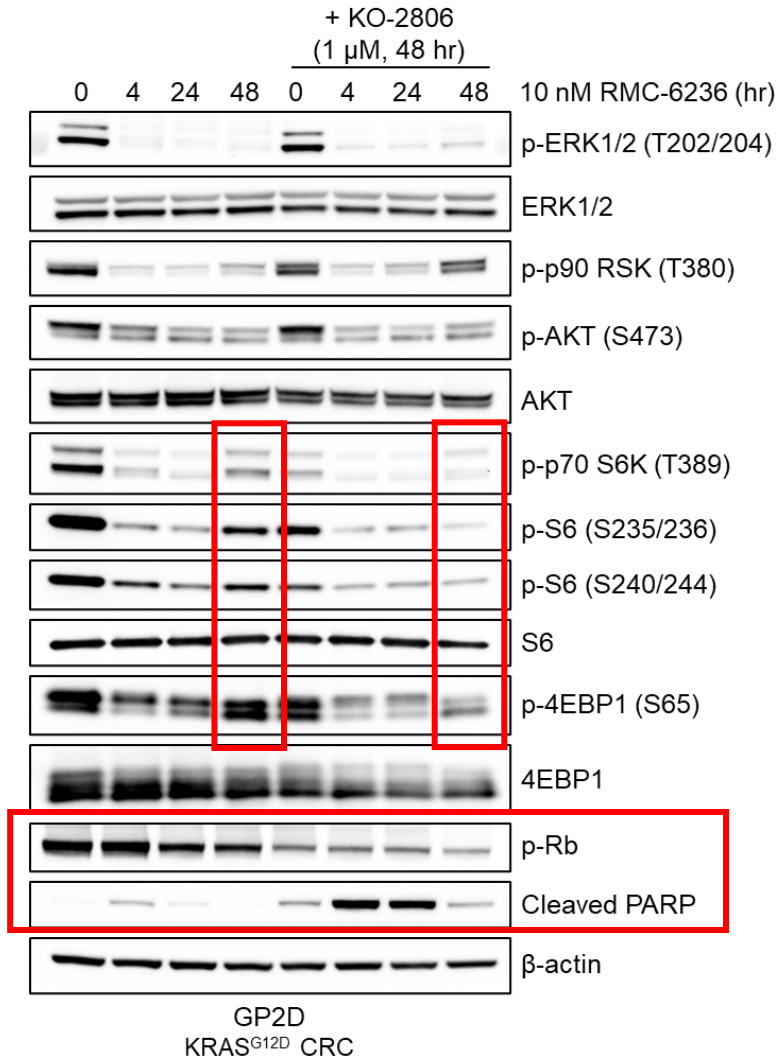




GP2D
KRAS^{G12D} CRC

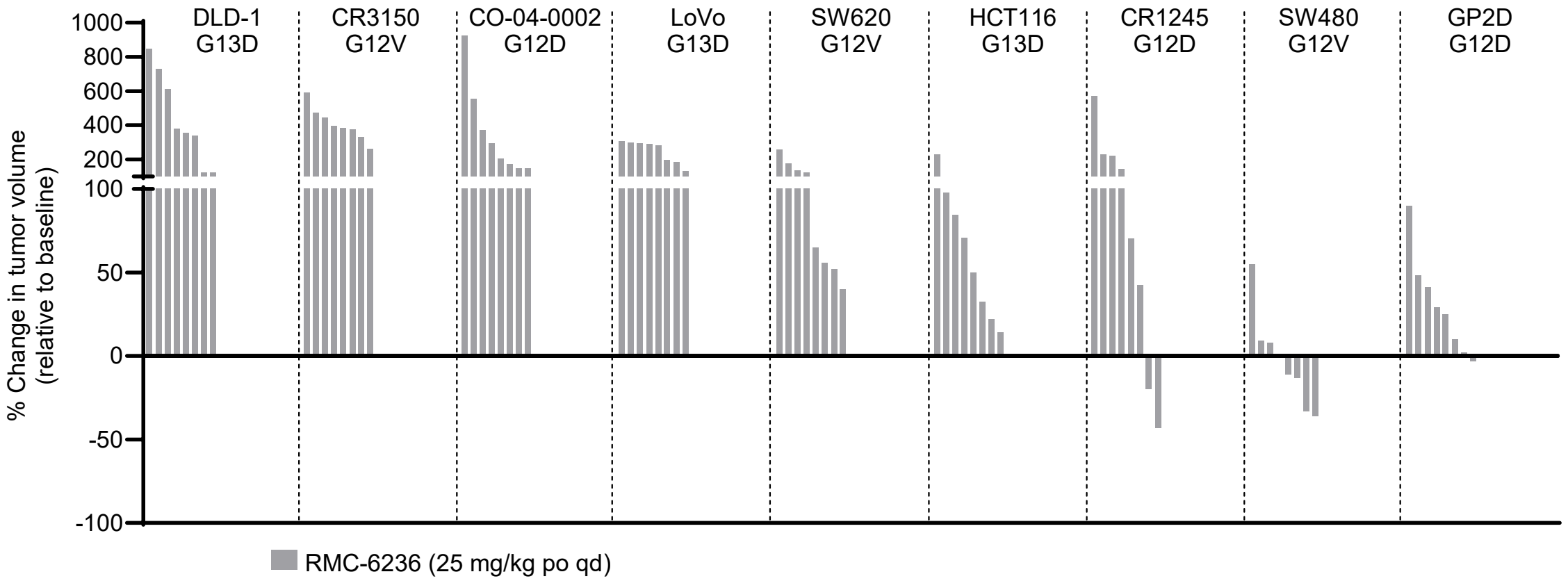
Persistent mTORC1 signaling remains a liability with pan-RAS inhibition and is targetable with the FTI KO-2806





Does this translate to *in vivo* combination activity?

Preclinical models of *KRAS*-mutant CRC are largely resistant to pan-RASi



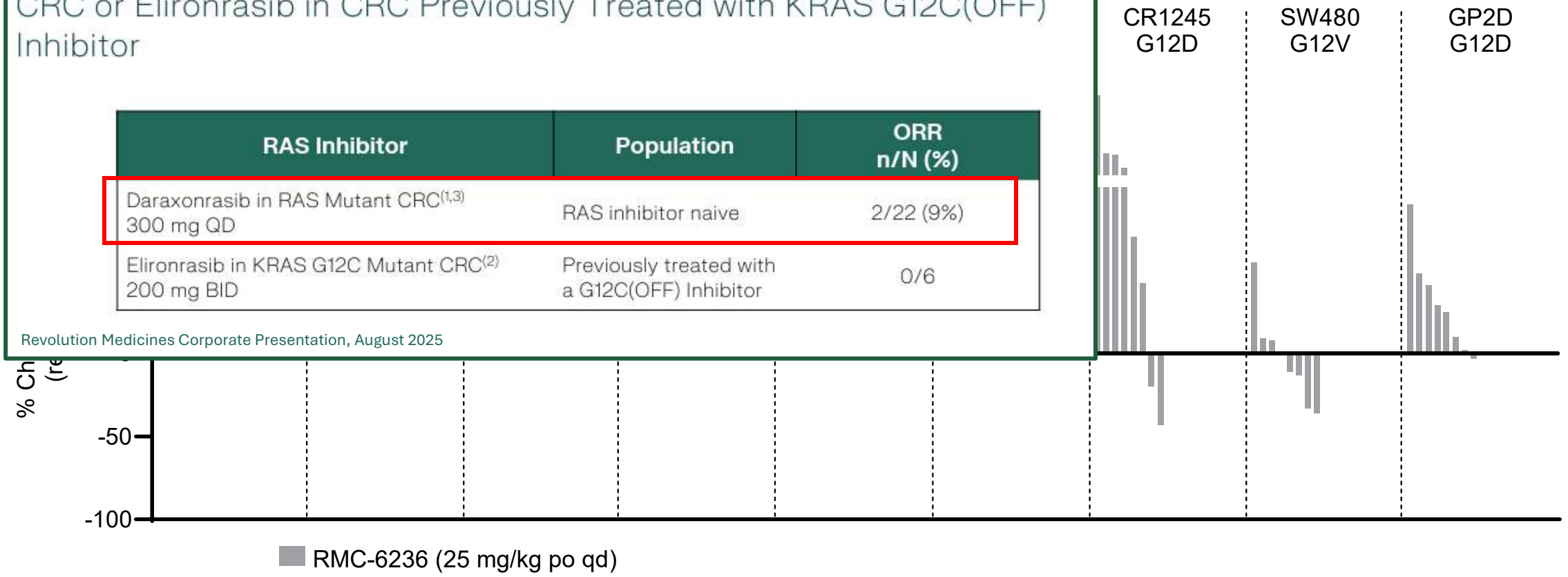
Preclinical models of *KRAS*-mutant CRC are largely resistant to pan-RASi

Consistent with preliminary clinical data

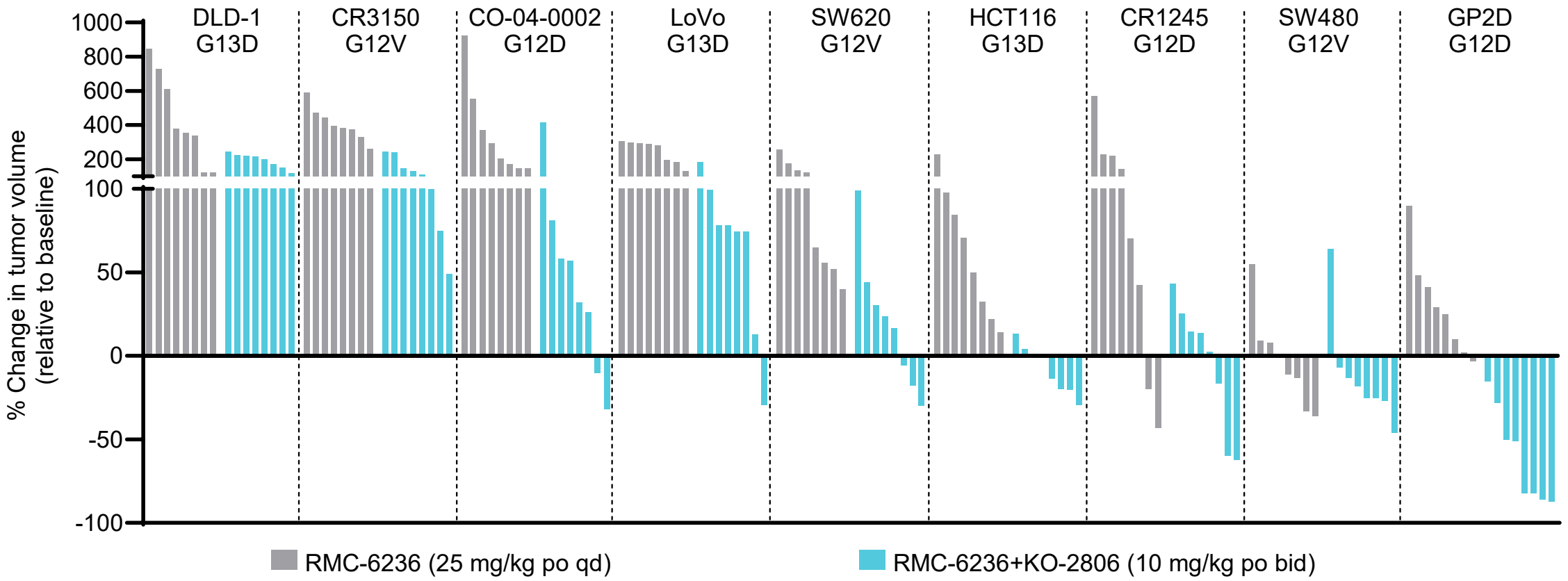
Limited Monotherapy Activity of Either Daraxonrasib in RAS Mutant CRC or Elironrasib in CRC Previously Treated with KRAS G12C(OFF) Inhibitor

RAS Inhibitor	Population	ORR n/N (%)
Daraxonrasib in RAS Mutant CRC[1,3] 300 mg QD	RAS inhibitor naive	2/22 (9%)
Elironrasib in KRAS G12C Mutant CRC[2] 200 mg BID	Previously treated with a G12C(OFF) Inhibitor	0/6

Revolution Medicines Corporate Presentation, August 2025

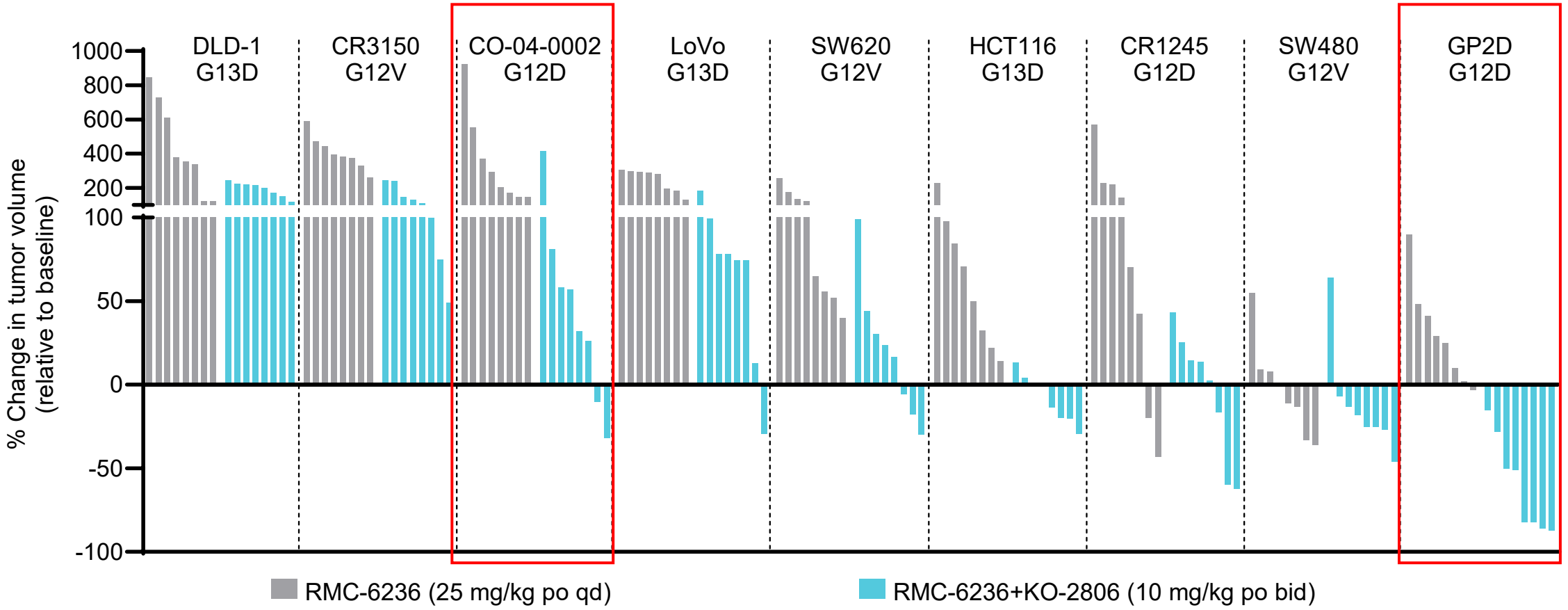


KO-2806 enhances antitumor activity of RMC-6236 in preclinical CRC xenograft models

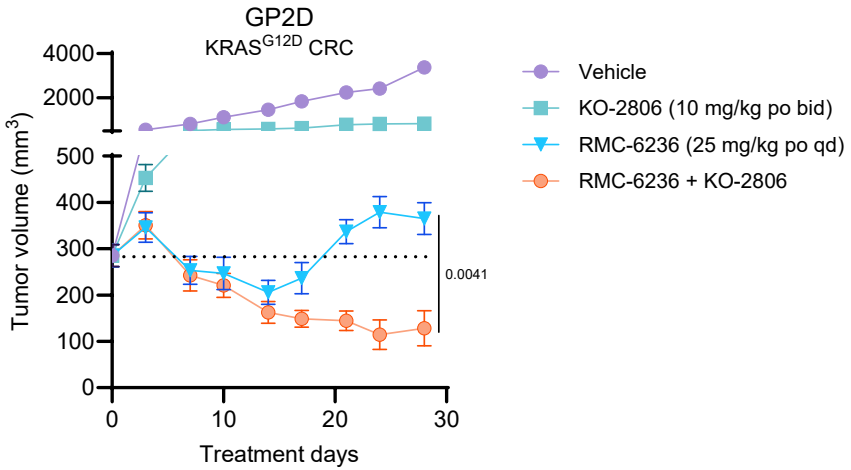


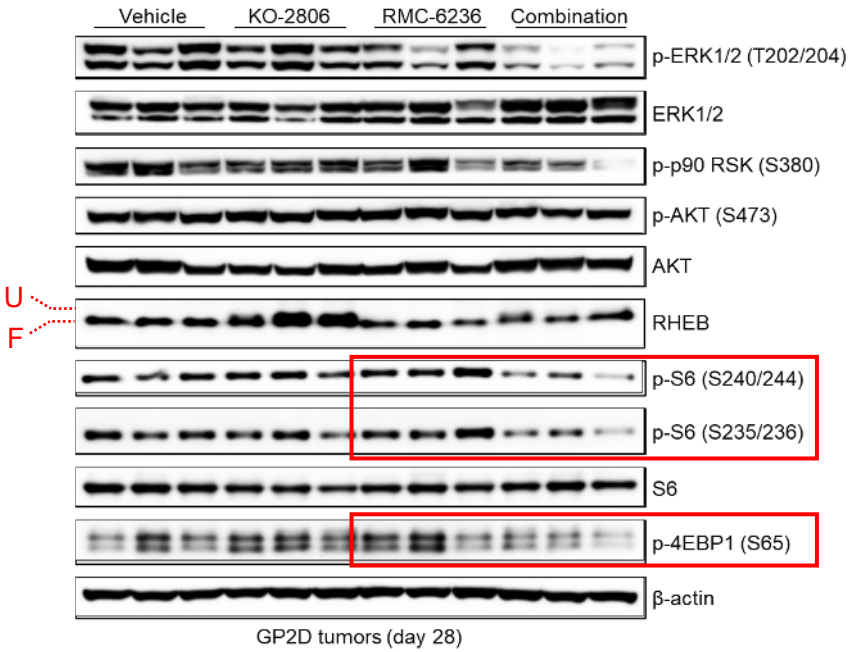
KO-2806 enhances antitumor activity of RMC-6236 in preclinical CRC xenograft models

What is the mechanism underlying this enhancement?

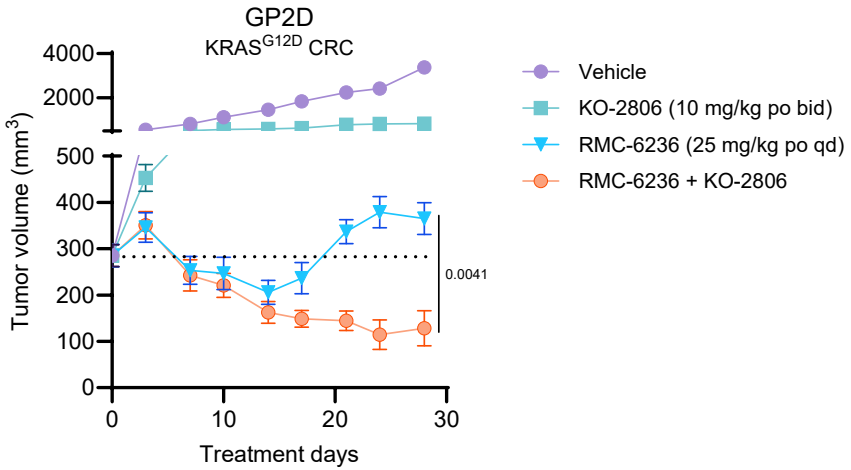


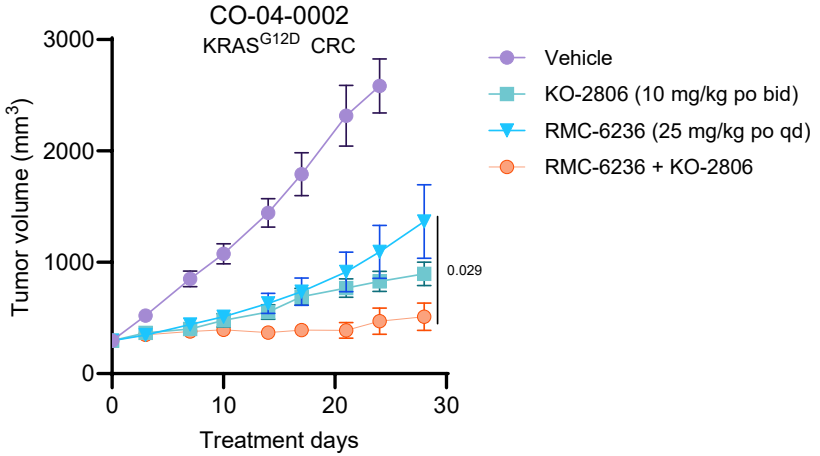
Enhanced tumor growth inhibition by pan-RAS/KO-2806 combination correlates with deeper mTORC1 inhibition *in vivo*

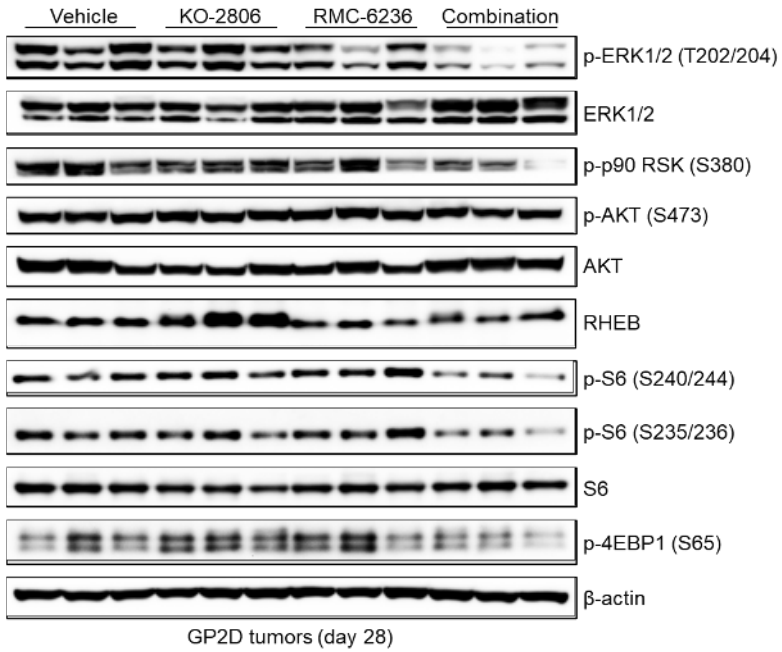




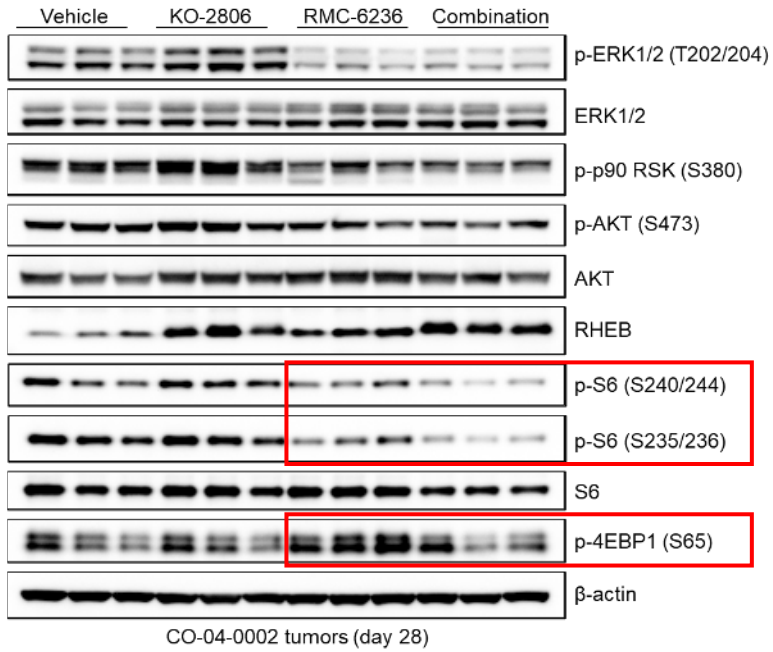
Enhanced tumor growth inhibition by pan-RAS/KO-2806 combination correlates with deeper mTORC1 inhibition *in vivo*





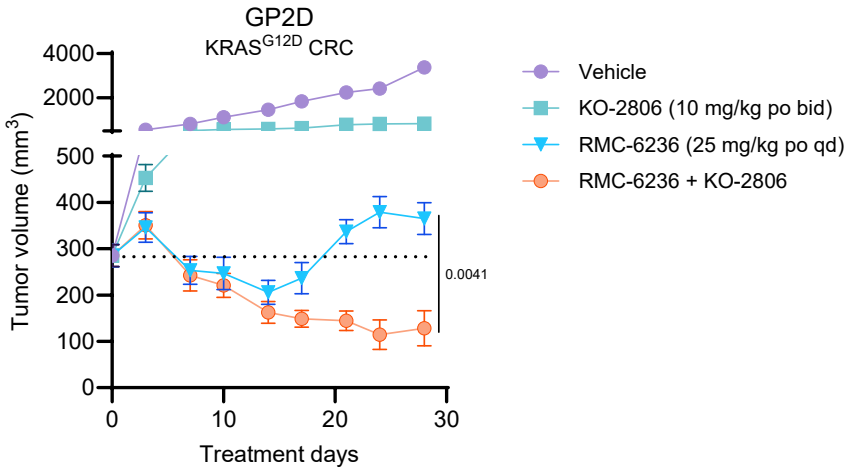


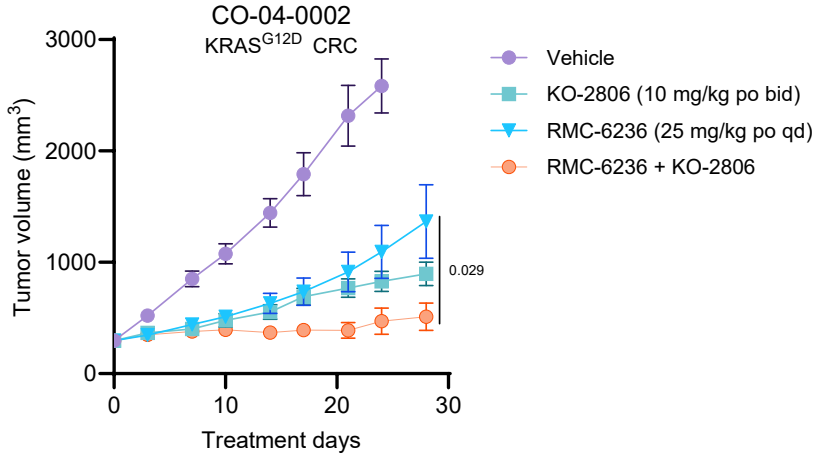
GP2D tumors (day 28)

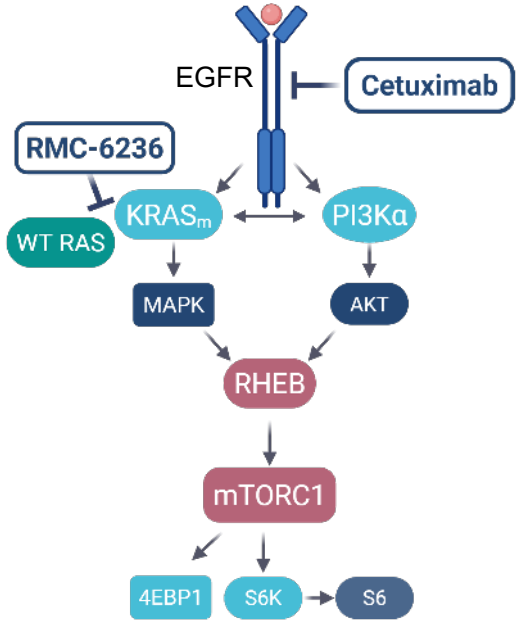


CO-04-0002 tumors (day 28)

Enhanced tumor growth inhibition by pan-RASi/KO-2806 combination correlates with deeper mTORC1 inhibition *in vivo*



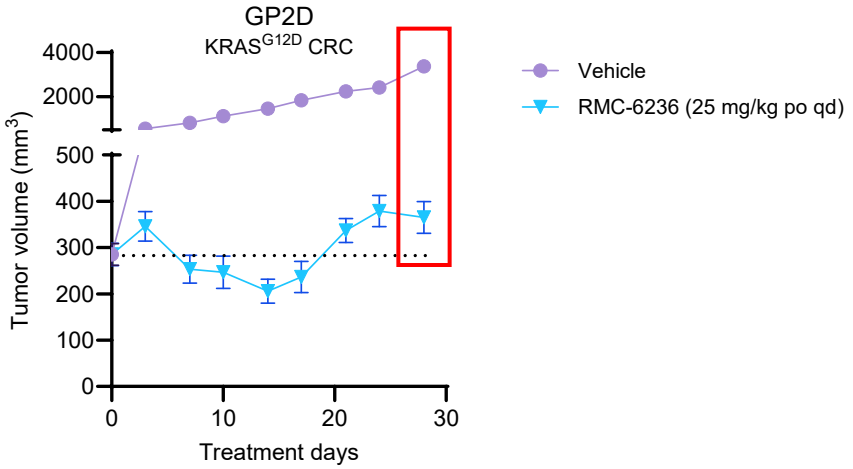


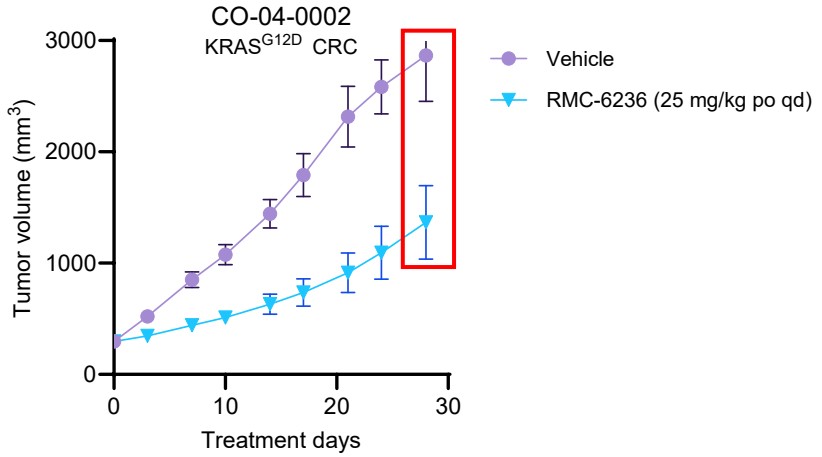


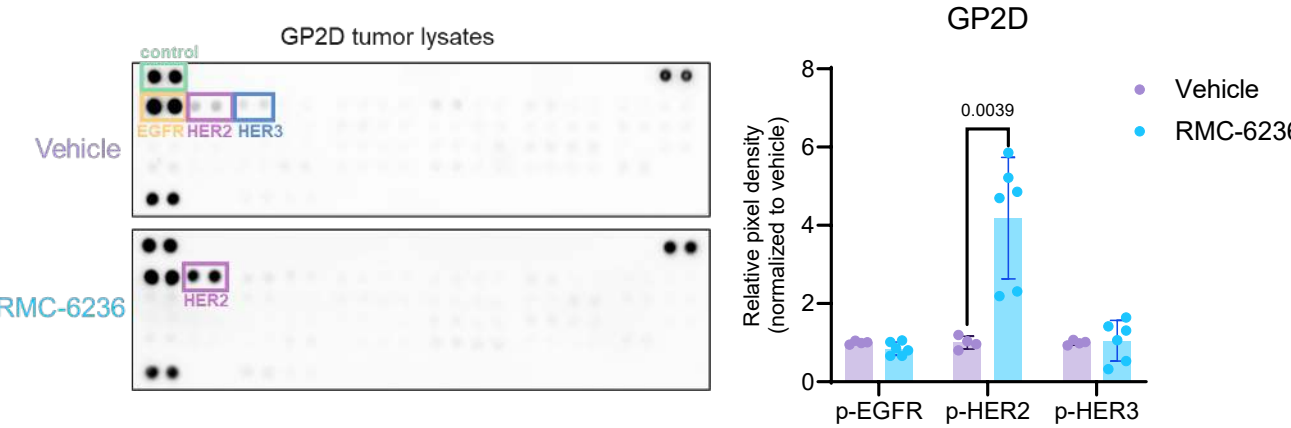
How does the pan-RAS/FTI combination compare to combined pan-RAS/EGFRi?

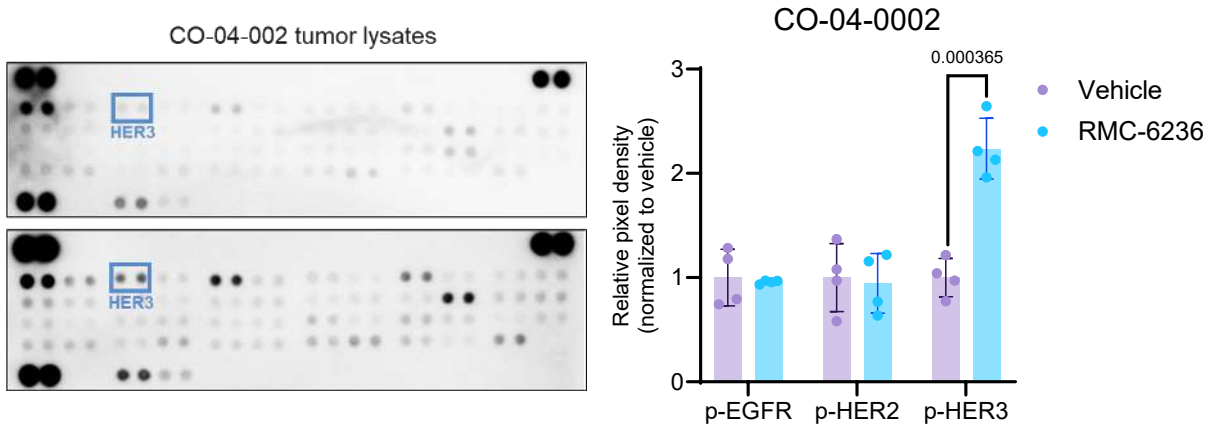
Is EGFR the dominant RTK mediating signaling reactivation/resistance to pan-RASi?

Pan-RAS inhibition induces the activity of multiple HER-family receptors *in vivo*

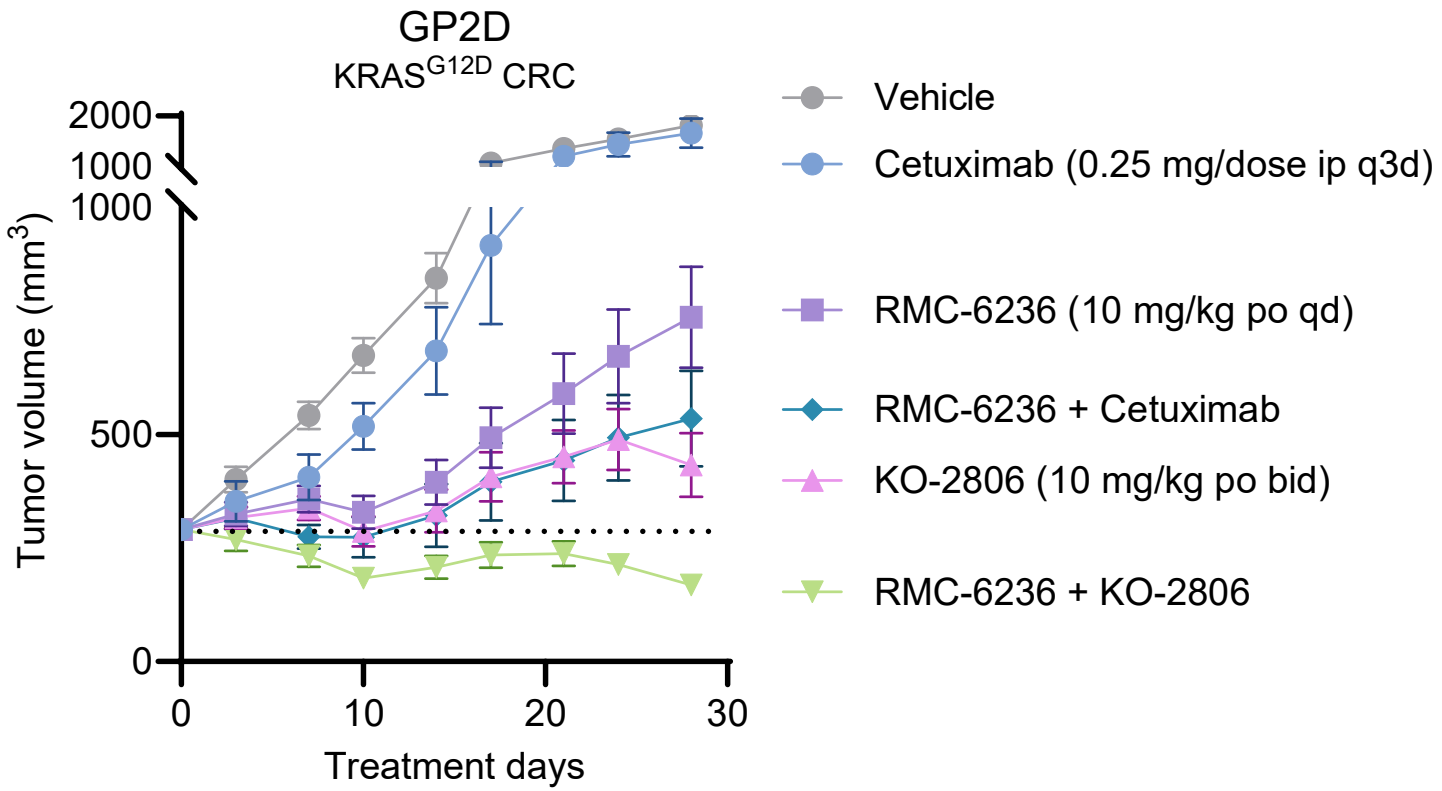






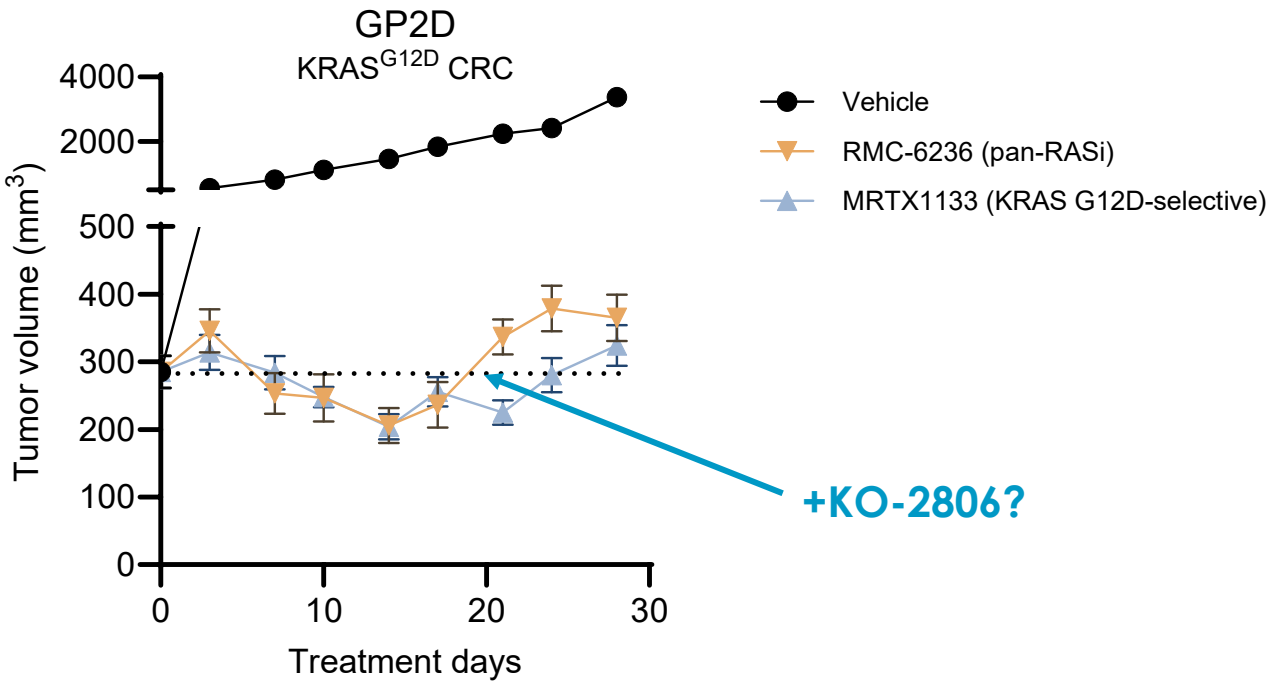


KO-2806/pan-RAS combination is superior to cetuximab/pan-RAS combination in GP2D CRC CDX model

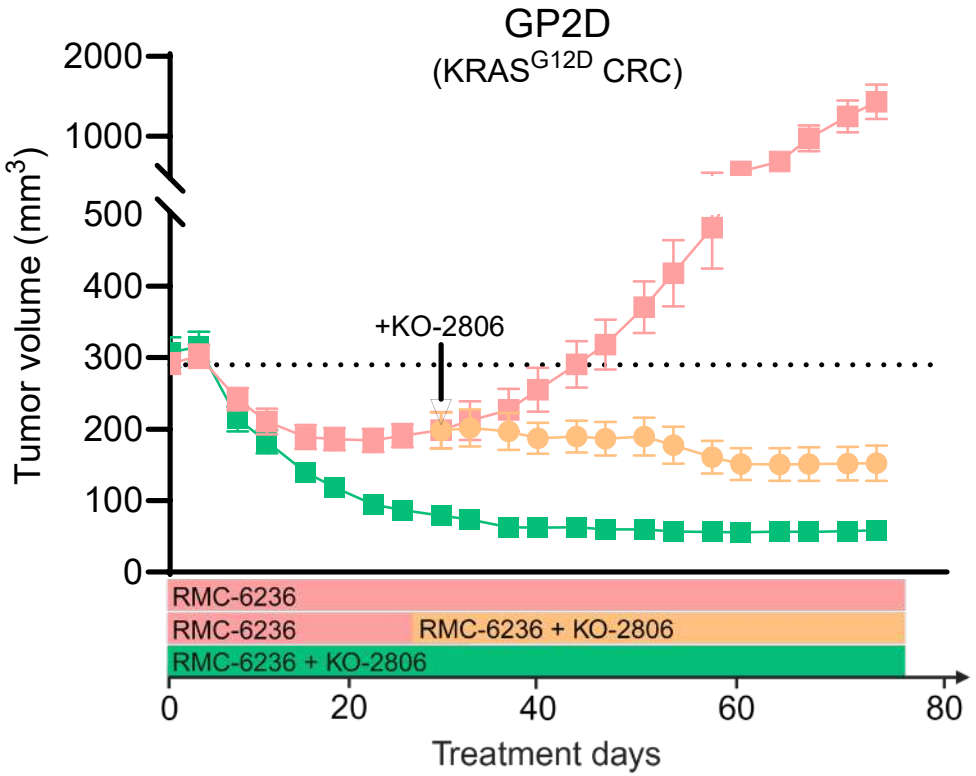


Potential benefit of KO-2806 in CRC tumors relapsing on pan- or mutant-selective RAS inhibitors

Is upfront co-administration required to enhance tumor growth inhibition?

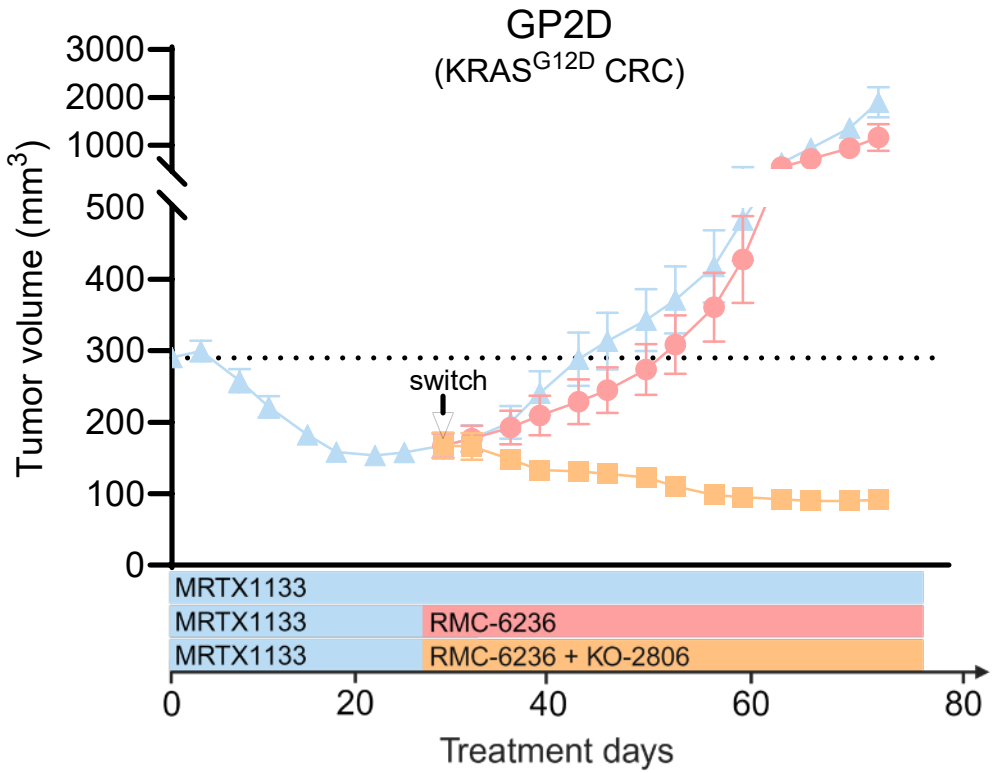


KO-2806 re-sensitizes CRC xenograft tumors relapsing on pan-RAS inhibitor; similar responses to upfront administration



25 mg/kg RMC-6236
10 mg/kg KO-2806

KO-2806 sensitizes CRC xenograft tumors relapsing on mutant-selective inhibitor to pan-RASi



10 mg/kg MRTX-1133
10 mg/kg KO-2806

Conclusions

- Reactivation of mTORC1 signaling remains a liability of pan-RAS inhibitors that is targetable by KO-2806, enhancing antitumor effects in preclinical models of CRC
- Basal EGFR activity is high in CRCs and pan-RASi induces additional HER-family receptors. As such, the combination of RMC-6236 and cetuximab is ineffective at controlling growth of CRC tumors while RMC-6236 and KO-2806 combination induces regressions
- CRC tumors relapsing on mutant-selective or pan-RAS inhibitors can be re-sensitized to pan-RAS inhibition by addition of KO-2806
- Given its ability to control persistent mTORC1 signaling mediated by elevated RTK activity in CRC, KO-2806 holds promise as a versatile combination treatment to augment the therapeutic potential of mutant-selective and pan-RAS inhibitors regardless of prior RAS-inhibitor exposure.
- KO-2806 (darlifarnib) is under clinical investigation in combination with targeted therapies in the FIT-001 trial; see ESMO presentations #2601P and #981P