RAS(ON) Inhibitor In-pathway Combinations Maximize RAS Pathway Suppression and Drive Deep and Durable Antitumor Activity in KRAS Mutant CRC Models

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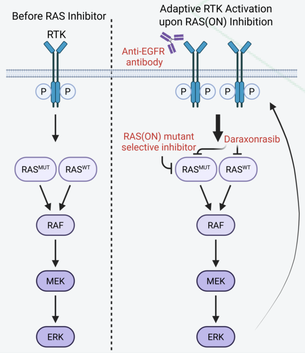
Introduction

RAS is one of the most frequently mutated oncogenes in colorectal cancer (CRC), occurring in ~50% of cases(1). Although the development and FDA approval of the KRAS G12C–selective inhibitors sotorasib (Lumakras) and adagrasib (Krazati) represent an important advance in the treatment of KRAS G12C-mutant non–small cell lung cancer (NSCLC)(2,3), the clinical benefit remains limited, and responses are often transient. In colorectal cancer, outcomes with these agents are even less favorable, with most patients experiencing disease progression within months(4,5). Moreover, most CRC patients harboring non-G12C RAS mutations such as RAS G12D/V still lack effective targeted therapies(1).

We have designed a series of tri-complex inhibitors that selectively target the GTP-bound, active state of RAS (RAS(ON)), thereby mitigating some of the resistance mechanisms observed with inactive state-selective inhibitors. These include daraxonrasib (RMC-6236), a RAS(ON) multi-selective noncovalent inhibitor of mutant and wild-type variants of the canonical RAS isoforms (K/N/H-RAS)(6) and the mutant-selective inhibitors elironrasib (RMC-6291)(7) and zoldonrasib (RMC-9805)(8) that covalently engage RAS(ON) G12C and RAS(ON) G12D, respectively. It has been published that major resistance mechanisms to RAS inhibition involve the reactivation of RAS pathway signaling in RAS mutant cancer cells(9,10). We hypothesize that increased therapeutic pressure on RAS signaling, via in-pathway combinations including RAS(ON) mutant-selective plus multi-selective inhibitor doublets and RAS(ON) inhibitor plus EGFR blockade, could enhance the antitumor activity in RAS mutant CRC.

Mechanistic Rationale for RAS(ON) Inhibitor In-pathway Combinations in KRAS Mutant CRC



Key Results

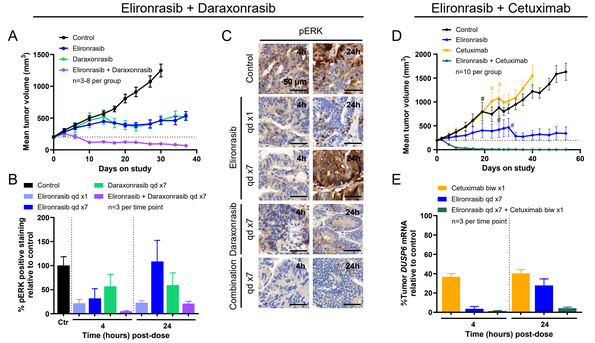
Preclinical Models Highlight Opportunity to Improve the Depth and Durability of Response to RAS(ON) Mutant-selective or Multi-selective Inhibitor Monotherapies in CRC

RAS(ON) inhibitor	NSCLC			PDAC			CRC		
	ORR	DCR	mTTD	ORR	DCR	mTTD	ORR	DCR	mTTD
Daraxonrasib(6)	52%	83%	NR	64%	91%	NR	26%	52%	60 days
Elironrasib(7)	72%	88%	NR	-	-	-	27%	47%	-
Zoldonrasib(8)	70%	80%	NR	78%	78%	NR	0%	57%	75 days

Overall response rate (ORR), disease control rate (DCR) and median time to tumor doubling (mTTD, as a surrogate for progression-free survival) of daraxonrasib, elironrasib and zoldonrasib in preclinical xenograft models harboring KRAS G12X, KRAS G12C and KRAS G12D mutations, respectively. mRECIST was applied to call the initial response as described previously(6). NR: not reached.

RAS(ON) Inhibitor Doublet and RAS(ON) G12C-Selective Inhibitor + Cetuximab Combinations Drive Deep and Sustained RAS Pathway Suppression and Tumor Regressions *In Vivo*

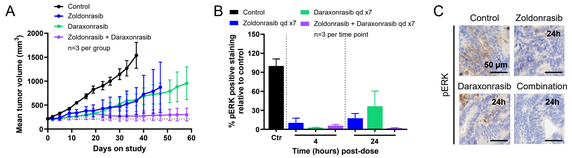
CRC022 PDX (*KRAS*$^{G12C/WT}$, CRC)



A, Antitumor activity of 100 mg/kg po qd elironrasib and 25 mg/kg po qd daraxonrasib as single agents or in combination in CRC022 subcutaneous PDX model. **B,** pERK IHC quantification post treatments of 30 mg/kg elironrasib and 25 mg/kg daraxonrasib as single agents or in combination. **C,** Representative pERK IHC images. **D,** Antitumor activity of 100 mg/kg po qd elironrasib and 20 mg/kg ip biw cetuximab as single agents or in combination. #: One mouse terminated due to tumor burden. **E,** *DUSP6* qPCR analysis post treatments of 30 mg/kg elironrasib and 20 mg/kg cetuximab as single agents or in combination.

RAS(ON) Inhibitor Doublet Leads to Sustained RAS Pathway Inhibition and Combinatorial Benefit in KRAS G12D CRC *In Vivo*

CRC043 PDX (*KRAS*$^{G12D/WT}$, CRC)

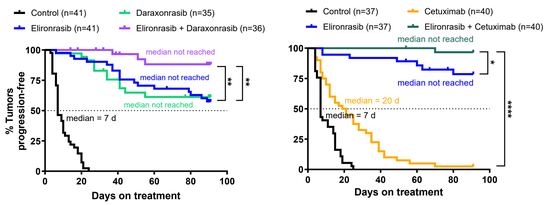


A, Antitumor activity of 100 mg/kg po qd zoldonrasib and 10 mg/kg po qd daraxonrasib as single agents or in combination in CRC043 subcutaneous PDX model. **B,** Quantification of pERK IHC post treatments of 100 mg/kg zoldonrasib and 10 mg/kg daraxonrasib as single agents or in combination. **C,** Representative pERK IHC images.

RAS(ON) Inhibitor Doublet and RAS(ON) G12C-Selective Inhibitor + Cetuximab Improve the Depth and Durability of Response Across a Panel of KRAS G12C CRC Models

Response rates	RAS(ON) multi-selective inhibitor	RAS(ON) G12C-selective inhibitor	RAS(ON) inhibitor doublet	RAS(ON) G12C-selective inhibitor + Cetuximab
ORR	44%	44%	76%	87%
DCR	67%	67%	94%	100%

Note: this table contains datasets from investigational agents and preclinical tool compounds.

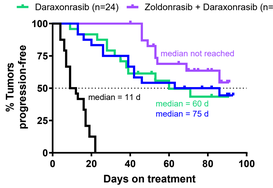


Table, ORR and DCR of RAS(ON) inhibitors (25 mg/kg po qd daraxonrasib, 10 mg/kg po qd RMC-7977 (preclinical tool compound for daraxonrasib), 30 or 100 mg/kg po qd elironrasib, and 30 mg/kg po qd RMC-4998 (preclinical tool compound for elironrasib)) as single agents, doublet combination or in combination with 20 mg/kg ip biw cetuximab in KRAS G12C subcutaneous CRC xenograft models. **Figure,** Kaplan-Meier analyses upon treatments. Log-rank test (*, P<0.05; **, P<0.01; ****, P < 0.0001).

RAS(ON) Inhibitor Doublet and RAS(ON) G12D-Selective Inhibitor + Cetuximab Improve the Depth and Durability of Response Across a Panel of KRAS G12D CRC Models

Response rates	RAS(ON) multi-selective inhibitor	RAS(ON) G12D-selective inhibitor	RAS(ON) inhibitor doublet	RAS(ON) G12D-selective inhibitor + Cetuximab
ORR	8%	15%	40%	38%
DCR	38%	54%	100%	100%

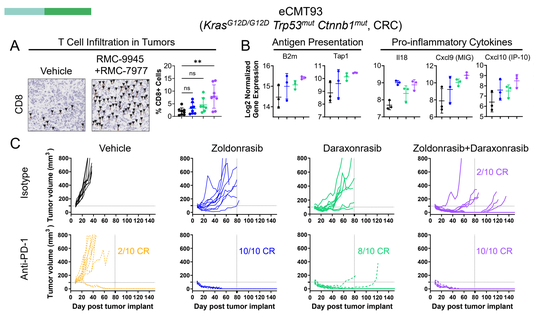
Note: this table contains datasets from investigational agents and preclinical tool compounds.



Table, ORR and DCR of RAS(ON) inhibitors (25 mg/kg po qd daraxonrasib, 10 mg/kg po qd RMC-7977, 100 mg/kg po qd zoldonrasib, 100 mg/kg po qd RMC-9945 (preclinical tool compound for zoldonrasib)) as single agents, doublet combination or in combination with 20 mg/kg ip biw cetuximab in KRAS G12D CRC subcutaneous xenograft models. **Figure,** Kaplan-Meier analyses upon daily treatments.

The RAS(ON) Inhibitor Doublet Maximizes the Favorable Modulation of TME and Synergizes With anti-PD-1 in a Syngeneic Model of MSS KRAS G12D CRC

eCMT93 (*Kras*$^{G12D/G12D}$ *Trp53*^{mut} *Ctnnb1*^{mut}, CRC)



A, Representative CD8 IHC images and quantification post 4 consecutive daily doses of vehicle control and 100 mg/kg RMC-9945 + 25 mg/kg RMC-7977. Black arrows indicate CD8+ T cells in the tumor core. One-way ANOVA (**, P<0.01). **B,** Transcriptomic analysis of whole tumor tissue. **C,** Antitumor activity of RAS(ON) inhibitors (100 mg/kg po qd zoldonrasib and 25 mg/kg po qd daraxonrasib as single agents and in combination) +/- 10 mg/kg ip biw anti-PD-1. Horizontal dotted line indicates initial tumor size. Vertical dotted line indicates treatment stop. CR = Complete regression.

Conclusions

- Reactivation of RAS pathway signaling is one of the major resistance mechanisms to RAS inhibition in patients and often observed in RAS mutant CRC xenograft tumors.
- RAS(ON) inhibitor doublet and RAS(ON) inhibitor plus cetuximab combinations drive more sustained RAS pathway suppression than the respective monotherapies and improve the depth and durability of antitumor activity in RAS mutant CRC xenograft models.
- RAS(ON) inhibitor doublet favorably modulates the tumor microenvironment and synergizes with anti-PD-1 to achieve durable complete regressions in a syngeneic model of MSS KRAS G12D CRC.

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