Mechanisms of Resistance to the RAS(ON) Multi-Selective Inhibitor Daraxonrasib (RMC-6236) in RAS Mutant PDAC and Potential Resolution with RAS(ON) Combination Therapies

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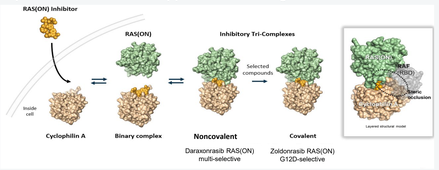
Introduction

- Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer that is driven by oncogenic RAS mutations in >90% of cases
- Daraxonrasib (RMC-6236) is an orally bioavailable RAS(ON) multi-selective tri-complex inhibitor with broad-spectrum activity against oncogenic mutant and wild-type variants of K, N and HRAS[1]
- We previously reported in an investigational study encouraging efficacy with acceptable safety/tolerability for daraxonrasib in patients with previously treated, RAS mutant metastatic PDAC, with a median progression-free survival (PFS) of 8.5 months (95% CI, 5.9 to NE) and overall survival (OS), NE (95% CI, 8.5 to not evaluable) at the dose of 300 mg (ct.gov NCT05379985)[2]. Based on these results, a randomized Phase 3 trial of daraxonrasib versus chemotherapy (RASolute 302, ct.gov NCT06625320) is underway
- Mechanisms of resistance to RAS(ON) inhibitors have not been elucidated and may be distinct from acquired resistance to KRAS G12C(OFF) inhibitors, where secondary oncogenic KRAS mutations have been observed
- Here, we report preclinical and clinical observations associated with acquired resistance to daraxonrasib in PDAC, and describe potential combination approaches to mitigate the mechanisms



RMC-6236-001 Phase 1 Design

Dose Escalation

Daraxonrasib administered orally QD to patients with RAS mutant disease including PDAC

Additional Method details can be accessed via poster QR code

400 mg
300 mg
220 mg*
160 mg
120 mg
80 mg
40 mg
20 mg
10 mg

Dose range explored for optimization,300 mg dose being used for Phase 3 RASolute 302 study

Lowest dose/exposure range projected to drive tumor regressions in humans based on preclinical models

Acquired resistance analyzed with paired baseline and end of treatment ctDNA using the Guardant Health Infinity assay in patients with previously treated, RAS mutant metastatic PDAC treated at 160 mg to 300 mg daraxonrasib with PFS > 3 months and subsequent progression

*220 mg was explored in escalation phase, while 200 mg was selected for further expansion/optimization. RMC-6236-001 Clinical Trial (ct.gov NCT05379985)

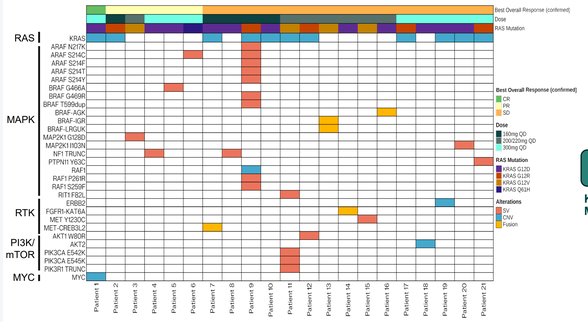
Identified Molecular Features and Mechanisms of Resistance Reactivate RAS Pathway Signaling

Acquired Genomic Alterations in ctDNA at Clinical Progression

Paired ctDNA Analysis in Patients with PDAC with Acquired Resistance in RMC-6236-001

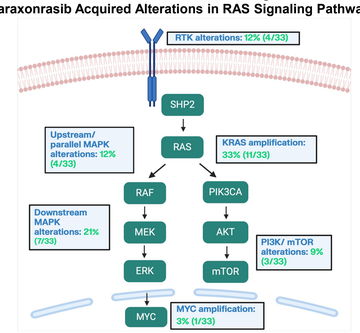
42 patients treated with 160 to 300 mg of daraxonrasib with PFS > 3 months who subsequently progressed → **33** patients with paired baseline and EOT sequenced successfully → **21** patients with acquired oncogenic alteration in RAS signaling pathways (RAS, MAPK, PI3K, MYC, RTK)

23 Jul 2024 Clinical Data Cut



An acquired alteration was defined as an "Oncogenic" or "Likely Oncogenic" variant annotated by OncoKB™ and not detected in pre-treatment ctDNA. SV = short variant, defined as single nucleotide variant (SNV) or short indel; CNV = copy number variant, defined as 'focal amplification' (for oncogenes) or 'homozygous deletion' (for tumor suppressor genes); Fusion = requires at least one of the partner genes to be in pathway of interest. TRUNC = variant resulting in predicted truncated protein, defined as nonsense mutation, splice site or indel. Pathways of interest were derived from Sanchez-Vega *et al*.[3]

A Majority of Patients Profiled with PDAC Disease Progression at 160 to 300 mg of Daraxonrasib Acquired Alterations in RAS Signaling Pathways



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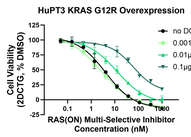
Initially sensitive KRAS mutant PDAC → Tumor evolution following daraxonrasib therapy → Acquisition of resistance features → Resistance features: KRAS Amp, alterations in MAPK and PI3K genes, RTKs, MYC amp

Preclinical Models Capture Genomic Mechanisms of RAS Pathway Reactivation

Mutant KRAS Amplification

KRAS Mutant Overexpression Confers Resistance to RAS(ON) Multi-Selective Inhibitor



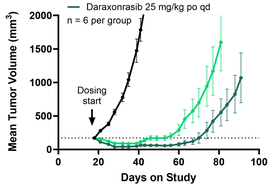
RAS

KRAS MYC

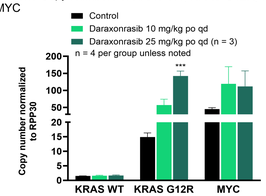
KRAS and MYC Amplification

KRAS G12R and MYC Amplifications in PDAC CDX Model with Acquired Resistance to Daraxonrasib

A. PSN-1 CDX Tumors Relapsed After Extended Treatment with Daraxonrasib



B. Gene Copy Numbers of KRAS WT, KRAS G12R, and MYC

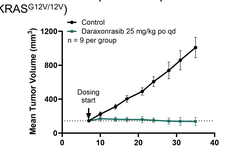


A. Mean tumor volume during extended treatment with daraxonrasib at 10 or 25 mg/kg qd. **B.** ddPCR analysis of PSN-1 xenograft tumors harvested at the end of treatment. Gene copy numbers were compared with control group using one-way ANOVA followed by Dunnett's multiple comparison test (***, $P < 0.001$).

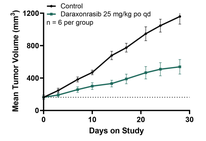
RTK Hyperactivation

Increased Levels of HER2, pEGFR in PDAC CDX Model with Acquired Resistance to Daraxonrasib

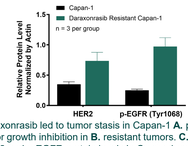
A. Daraxonrasib Response in Capan-1 Parental CDX Model (KRAS$^{G12V/12V}$)



B. Daraxonrasib Response in Capan-1 CDX Model of Acquired Resistance (KRAS$^{G12V/12V}$)



C. Increased Levels of HER2, p-EGFR in Capan-1 Model with Acquired Resistance to Daraxonrasib



Daraxonrasib led to tumor stasis in Capan-1 **A.** parental tumors and tumor growth inhibition in **B.** resistant tumors. **C.** Immunoblot analyses of HER2 and p-EGFR protein levels in Capan-1 parental and resistant tumors harvested at 4h post dosing on day 7.

Potential Combination Approaches

Potential combination options: RAS(ON) mutant-selective inhibitors, RTK inhibitors

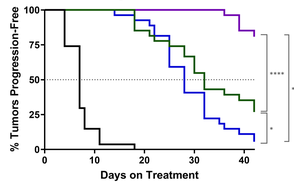
Initially sensitive KRAS mutant PDAC → Tumor evolution following daraxonrasib therapy → Acquisition of resistance features → Resistance features: KRAS Amp, alterations in MAPK and PI3K genes, RTKs, MYC amp

Mitigation of Increased Signaling Via Amplified Mutant KRAS by RAS(ON) Inhibitor Doublets

RAS(ON) Inhibitor Doublets Provide Durable Responses in Preclinical PDAC Models

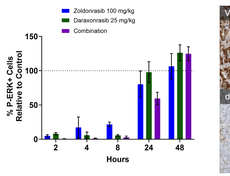
RAS

A. RAS(ON) Inhibitor Doublet Increases Progression-free Survival Benefit in KRAS G12D Allograft Models

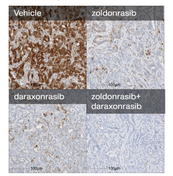


Control, n = 27, median 6d
Zoldonrasib 100 mg/kg po qd, n = 27, median 28d
Daraxonrasib 25 mg/kg po qd, n = 26, median 32d
Combination, n = 27, median not reached

B. RAS(ON) Inhibitor Doublet Further Inhibits Pathway Signaling in KPCYc3 (*KRAS$^{G12D/+}$; Trp53$^{LSL-R172H/+}$*)

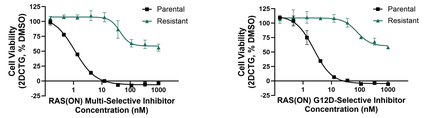


pERK IHC

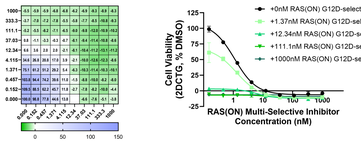


A. Three KPCY (*KRAS$^{G12D/+}$; Trp53$^{LSL-R172H/+}$* models: KPCYc3 (2838c3), c4 (6499c4), and c5(6419c5) derived as described in Li et al.[4] Progression defined as tumor doubling from baseline. Log-rank test (*p<0.05, ****P<0.0001). **B.** Percentage of P-ERK positivity relative to vehicle-treated control, measured by IHC in panCK+ tumor cells. N = 3 tumors per treatment group per timepoint after single dose of daraxonrasib, zoldonrasib, or the combination of both. Representative IHC images of P-ERK staining at 8h post dose.[5]

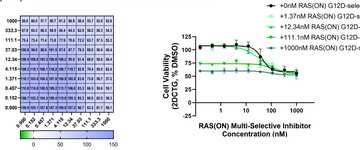
A. Cross-resistance to RAS(ON) Multi- and Mutant Inhibitors in the PDAC Model with KRAS G12D CN = 8



B. RAS(ON) Inhibitor Doublets in Parental Model



C. RAS(ON) Inhibitor Doublets in Resistant Model

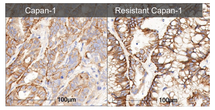


A. 5-day 2D cellular viability assay was performed with HPAC parental and resistant cell line to assess sensitivity to single agents RAS(ON) multi and G12D mutant-selective. 5-day 2D cellular viability assay was performed with HPAC parental (**B**) and resistant (**C**) cell lines to assess sensitivity to RAS(ON) inhibitor combination treatments. Data were presented in a matrix as % of DMSO and as dose response curves.

Targeting RAS Signaling Via Combination of Daraxonrasib with HER2 Inactivation

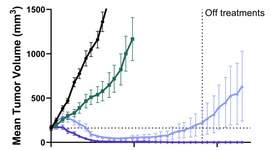
Daraxonrasib Combined with T-DXd Led to Deep and Durable Tumor Regression in Daraxonrasib Resistant Tumors

A. HER2 IHC Staining at 4h Post-dosing on Day 7



A. Representative IHC staining of HER2 in Capan-1 parental and daraxonrasib resistant tumors (n = 3 per group). **B.** Tumor-bearing mice were treated for 90 days followed by observation without treatments as indicated. Plots represent mean tumor volumes of each group. T-DXd (Trastuzumab Deruxtecan, DS-8201) is an anti-HER2 antibody-drug conjugate (ADC).[6]

B. Treatment Response in Capan-1 CDX Model of Acquired Resistance (KRAS$^{G12V/12V}$)



Conclusions

- Putative genomic mechanisms of acquired resistance were identified in a majority of patients with PDAC treated with daraxonrasib and eventual disease progression, with amplification of KRAS being the most common
- Other acquired alterations were found in RAF, RTKs, PI3K pathway genes and MYC and, in some cases, patients acquired multiple genomic alterations reactivating RAS pathway signaling
- Consistent with the broad RAS(ON) inhibitory activity of daraxonrasib no acquired secondary oncogenic KRAS mutations were observed in patients with PDAC who progressed on treatment. This is distinct from the clinical resistance mechanisms reported for mutant-selective KRAS G12C(OFF) inhibitors, albeit these have been described primarily for KRAS G12C mutant NSCLC and CRC
- Alterations driving daraxonrasib resistance in preclinical models *in vitro* and *in vivo* were consistent with clinical observations
- The combination of daraxonrasib with a RAS(ON) G12D-selective inhibitor zoldonrasib (RMC-9805) drove combinatorial activity and forestalled monotherapy resistance in a series of preclinical models of PDAC
- Additional rational-driven combination approaches to forestall and address resistance are being explored

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Abbreviations: BCA, bicinchoninic acid; CDX, cell line-derived xenograft; CI, confidence interval; CNV, copy number variant; CRC, colorectal cancer; ctDNA, circulating tumor DNA; CTG, Champions TumorGraft; ddPCR, droplet digital PCR; DMSO, dimethyl sulfoxide; DOX, doxycycline; EOT, end of treatment; p-ERK, phosphorylated extracellular signal-regulated kinase; gDNA, genomic DNA; HER2, human epidermal growth factor receptor 2; HPAC, human pancreatic adenocarcinoma; IHC, Immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; LDS, lithium dodecyl sulfate; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; MYC, Myc proto-oncogene protein; nM, nanomolar; NSCLC, non-small cell lung cancer; NE, not estimatable; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetics; PO, per os (by mouth); QD, quaque die (once a day); RAF, Raf-1 Proto-Oncogene, Serine/Threonine Kinase; RAS, rat sarcoma; RPP30, ribonuclease P protein subunit p30; RTK, receptor tyrosine kinase; SV, short variant, defined as single nucleotide variant (SNV) or short indel; TDxD, T-DXd trastuzumab deruxtecan; VAF, variant allele frequency; VUS, variant of uncertain significance

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Revolution Medicines Research and Development Teams

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