



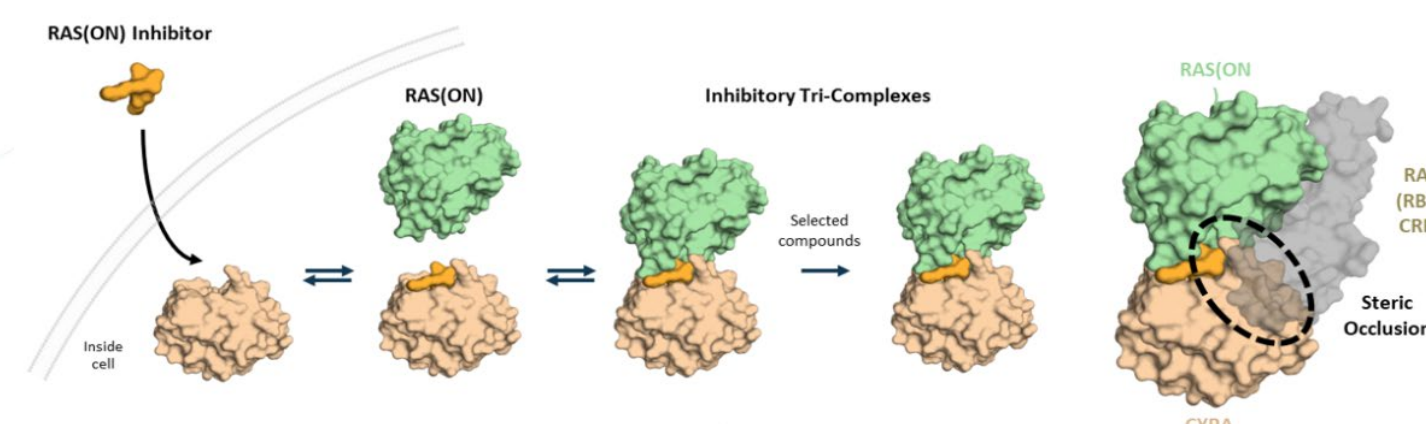
Resistance Mechanisms to Monotherapy RAS(ON) Multi-Selective Inhibitor Daraxonrasib (RMC-6236) in RAS Mutant PDAC Inform Therapeutic Combination Strategies

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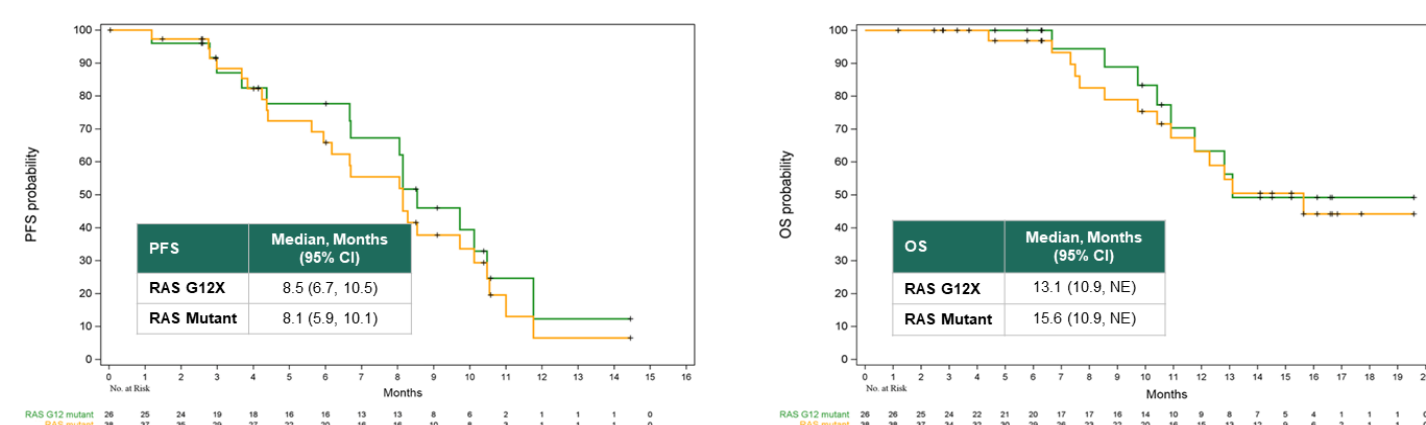
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Introduction

- 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 HRAS¹
- We previously reported in an investigational study encouraging efficacy with acceptable safety/tolerability for daraxonrasib in patients with previously treated, RAS mutant metastatic PDAC (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 KRAS mutations have been observed³
- Here, we report preclinical and clinical observations associated with acquired resistance to daraxonrasib in PDAC, and describe potential combination approaches to mitigate the mechanisms

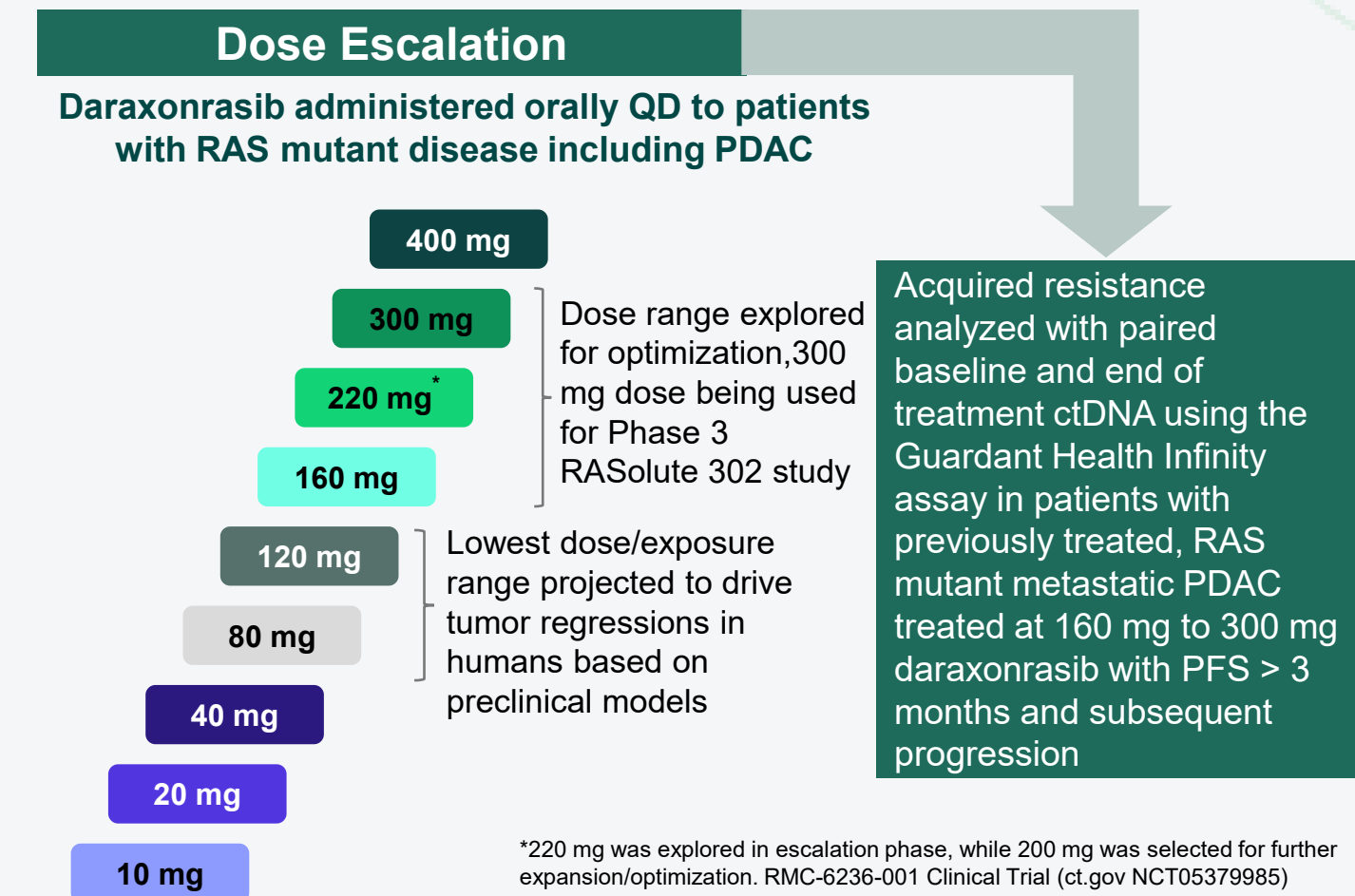


2L PDAC: Daraxonrasib RAS(ON) Multi-Selective Inhibitor (300 mg) Demonstrated Encouraging Progression-Free Survival and Overall Survival



Median (range) follow-up is 16.7 (10.3, 24.6) months and 17.4 (10.3, 24.6) months for RAS G12X and RAS Mutant, respectively. 2L, second line; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; CI, confidence interval.

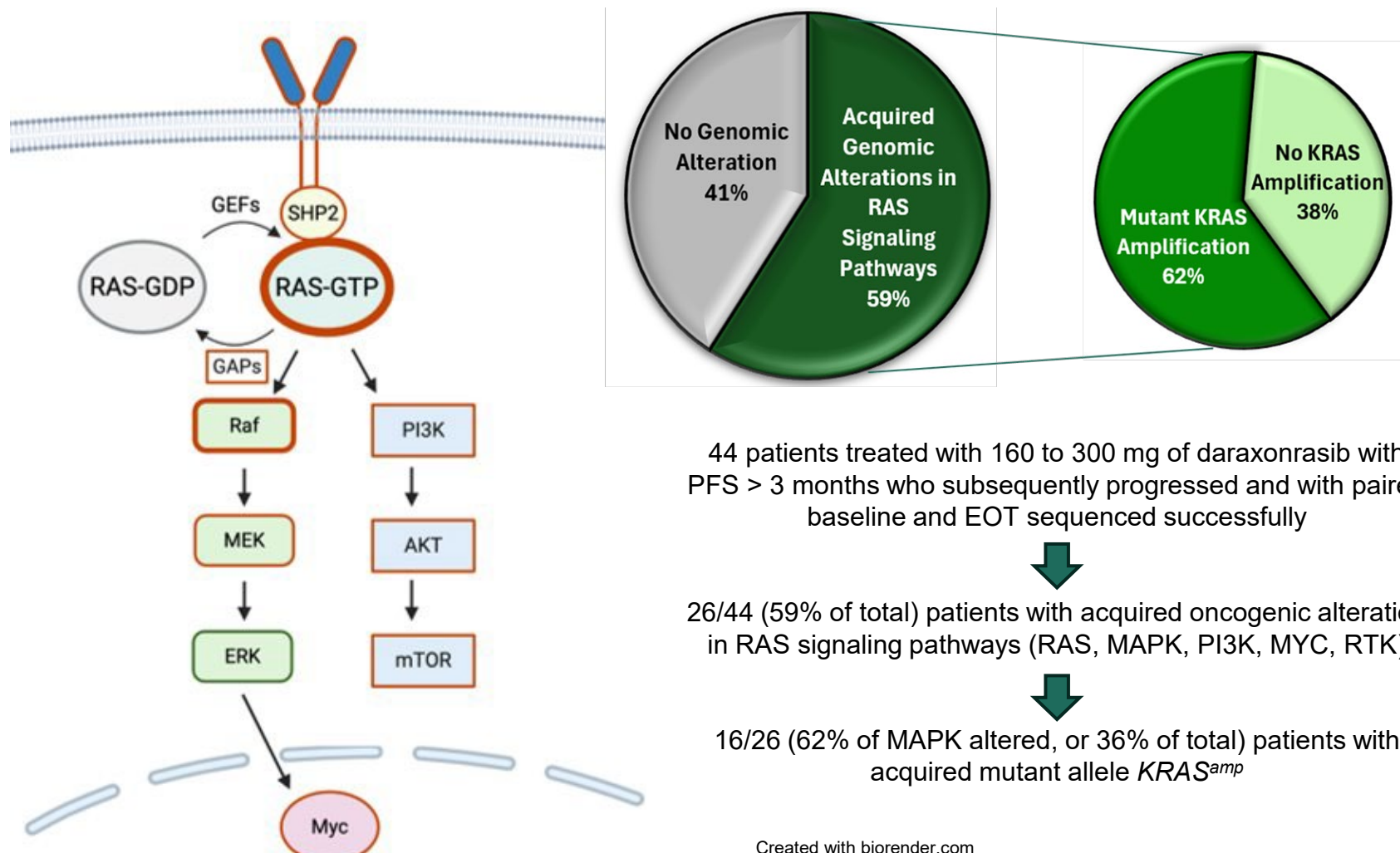
RMC-6236-001 Phase 1 Design



Identified Molecular Features and Mechanisms of Resistance Reactivate RAS Pathway Signaling

Acquired Genomic Alterations in ctDNA at Clinical Progression

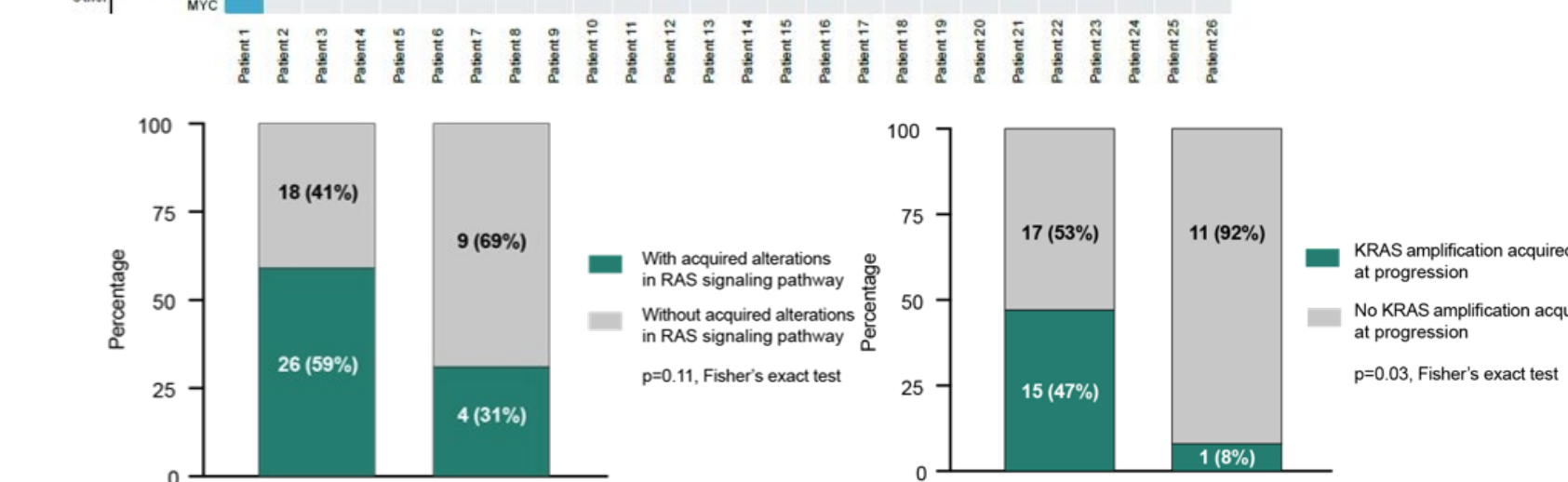
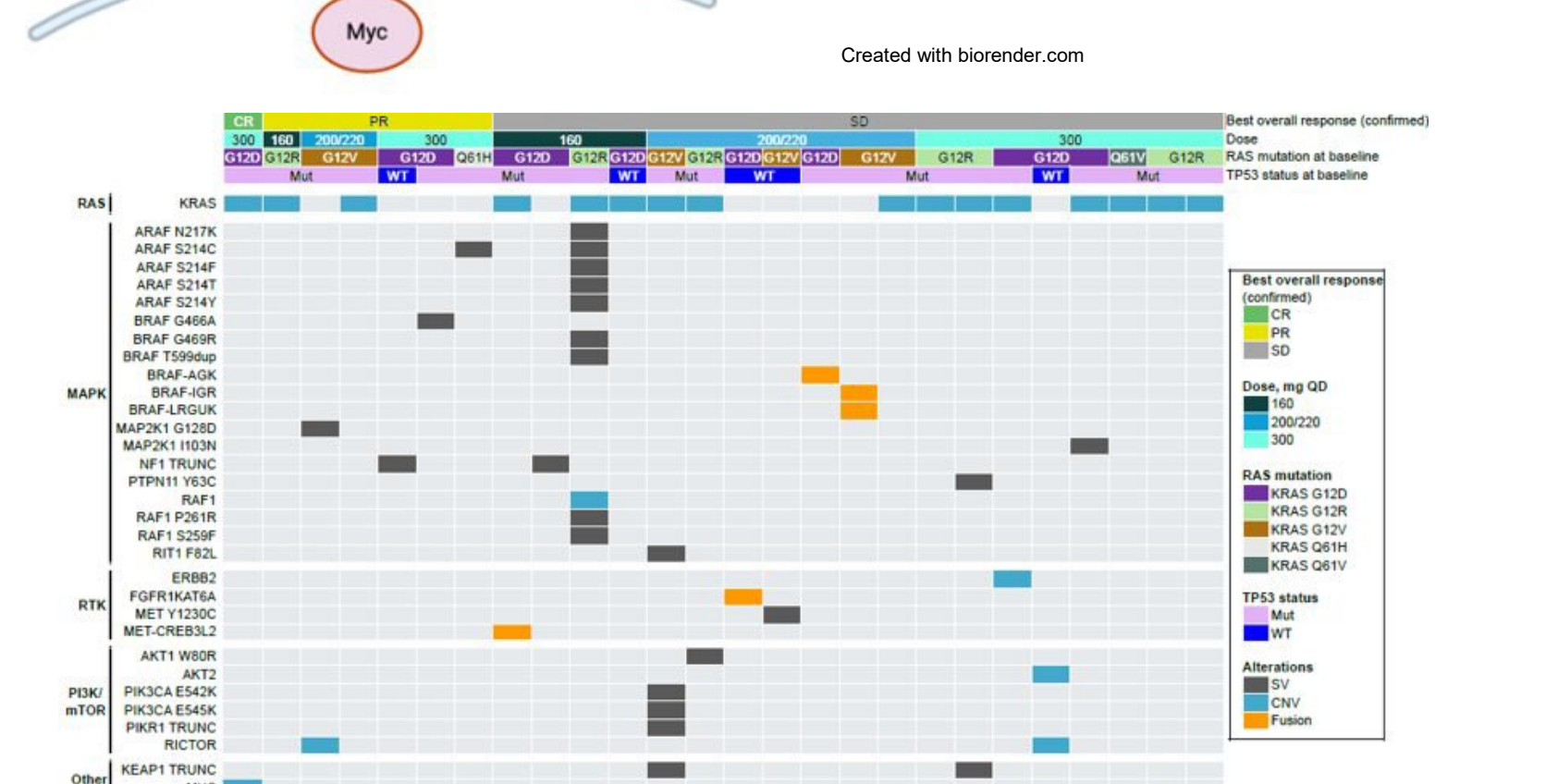
A Majority of Patients Profiled with PDAC Disease Progression at 160 to 300 mg of Daraxonrasib Acquired Alterations in RAS Signalling Pathways



44 patients treated with 160 to 300 mg of daraxonrasib with PFS > 3 months who subsequently progressed and with paired baseline and EOT sequenced successfully

26/44 (59% of total) patients with acquired oncogenic alteration in RAS signaling pathways (RAS, MAPK, PI3K, MYC, RTK)

16/26 (62% of MAPK altered, or 36% of total) patients with acquired mutant allele KRAS^{G12R}

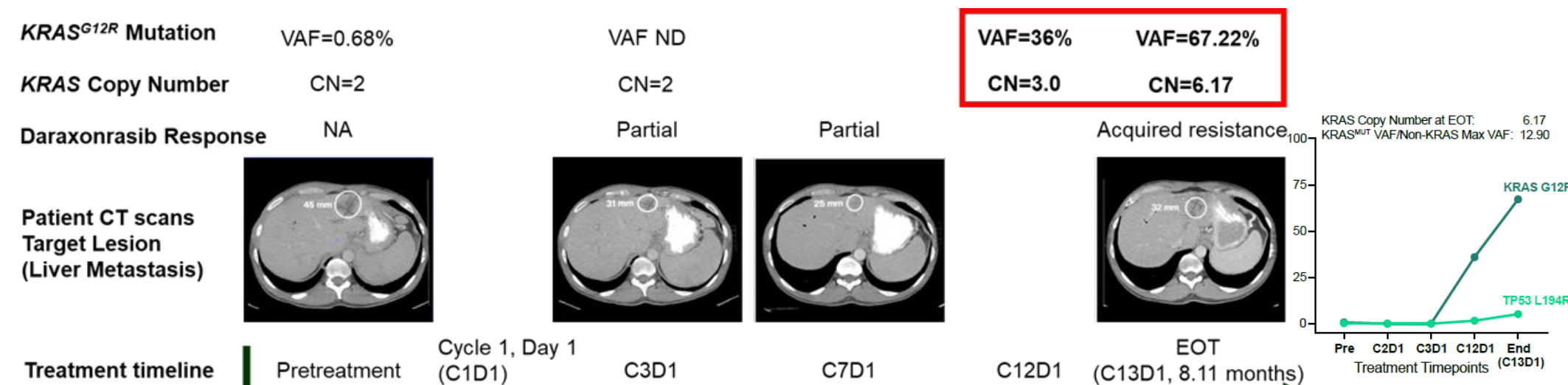


An acquired alteration was defined as an 'Oncogenic' or 'Likely Oncogenic' variant annotated by OncoKBTM and not detected in pre-treatment ctDNA. Putative acquired genomic resistance mechanisms were identified in a majority of the 44 patients profiled. SV = short variant, defined as single nucleotide variant (SNV) or short indel; CNV = copy number variant, defined as 'focal amplification' (for oncogenes) or 'homologous deletion' (for tumor suppressor genes); copy number above 2 is defined as amplification; 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. Relative ratio > 1 for mutant KRAS VAF relative to other somatic mutations was observed in all 16 patients with KRAS amp at progression, indicating that the mutant KRAS allele present prior to therapy is amplified in each case

Conclusions

- Analysis of pre- and end of treatment ctDNA samples from 44 PDAC patients treated with daraxonrasib for >3 months revealed prospective mechanisms of resistance**
 - 59% of patients had alterations in genes in the RAS signaling pathway, but no acquired oncogenic secondary KRAS mutations were observed, distinct from resistance profiles reported for mutant-selective KRAS G12C(OFF) inhibitors
 - Mutant KRAS amplification was the most prevalently observed alteration in 36% of patients; other genomic alterations included mutations in RTKs, MAPK and PIK3CA pathway members and MYC amplification
- Daraxonrasib monotherapy resistance mechanisms validated in preclinical models**
 - Mutant KRAS amplification or overexpression reduces daraxonrasib activity
 - Daraxonrasib induces increased HER2 expression and combines with trastuzumab-deruxetecan (T-DXd) to drive deep and durable activity in a daraxonrasib-resistant PDAC model
 - RAS(ON) inhibitor doublets drive deeper and more durable inhibition of tumor growth in parental and daraxonrasib-resistant PDAC tumor models
- A registrational clinical trial, RASolute 302 (NCT06625320), is currently ongoing to evaluate daraxonrasib as a 2L treatment for patients with metastatic pancreatic ductal adenocarcinoma (PDAC)**

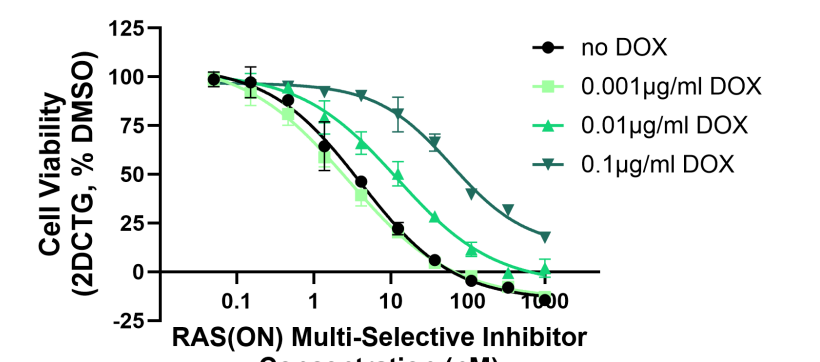
Case Study: Mutant KRAS^{G12R} Precedes Progression Following Durable Response to Daraxonrasib



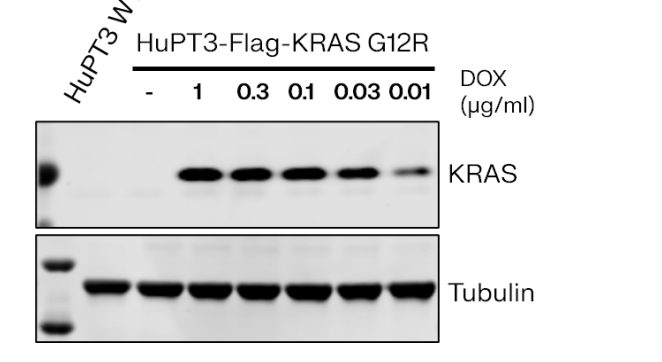
Preclinical Models Capture Genomic Mechanisms of RAS Pathway Reactivation

A. RAS Overexpression Attenuates Daraxonrasib Response *in vitro*

HuPT3 KRAS G12R Overexpression

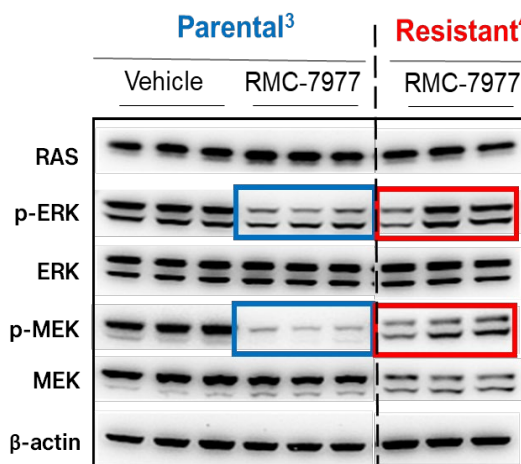
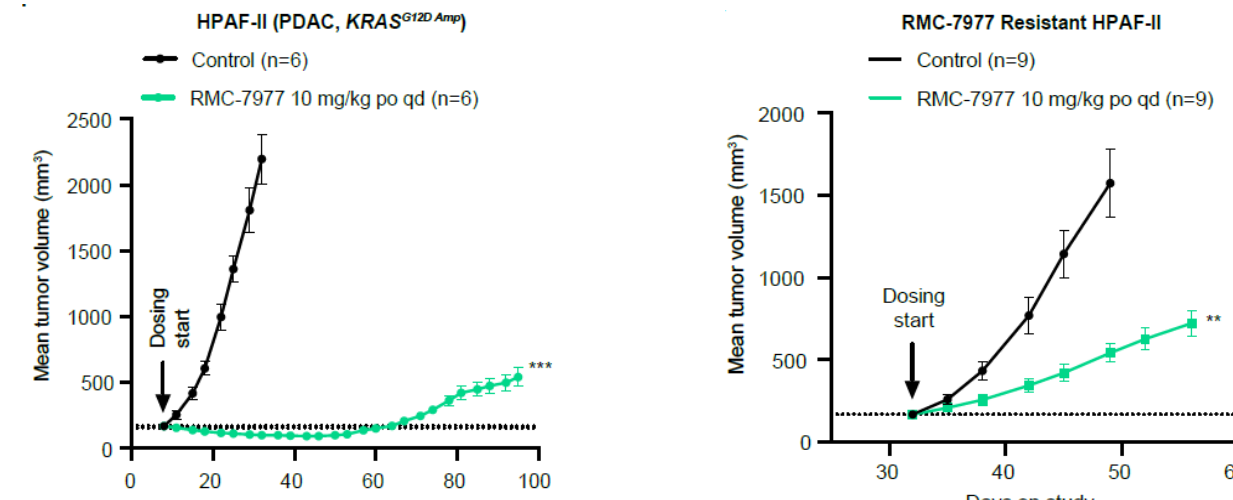


A, 5-day cellular viability assay was performed with the engineered HuPT3 cell line that has doxycycline (DOX)-inducible KRAS G12R overexpression

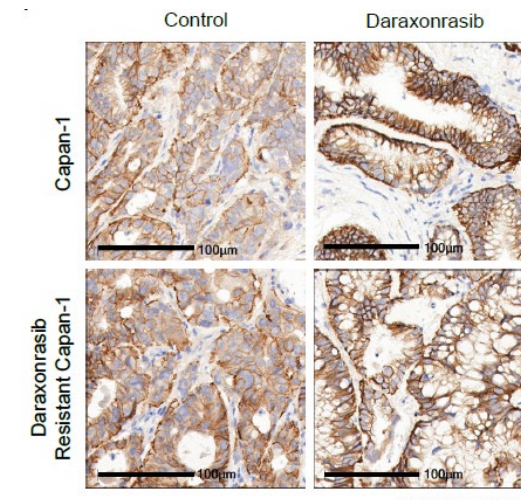
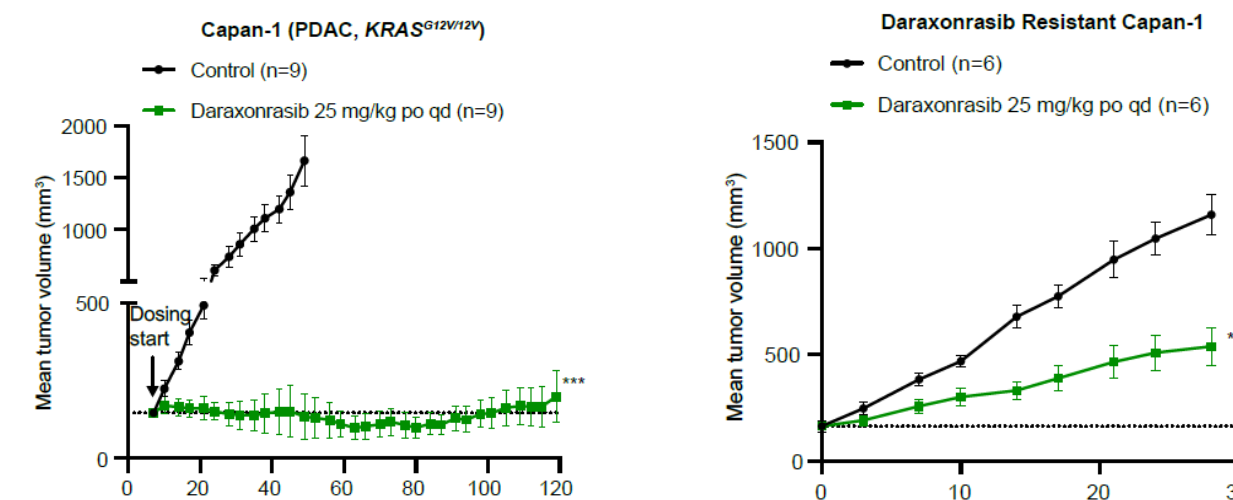


Western blots measuring the KRAS protein level from cells treated with the indicated concentration of Dox for 24 hours in the HuPT3 model

B. Resistance to RAS(ON) Multi-Selective Tool Molecule, RMC-7977, via RAS Pathway Reactivation in HPAF-II



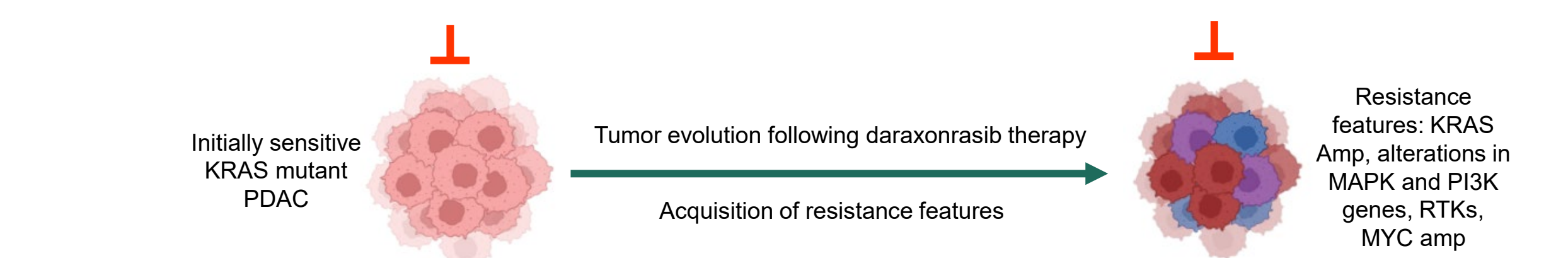
C. Capan-1 Daraxonrasib-Resistant CDX Model Demonstrates Treatment-Induced HER-2 Upregulation



B, C. Left Panels: The HPAF-II and Capan-1 tumor models resistant to RMC-7977 (10 mg/kg po qd) or daraxonrasib (25 mg/kg po qd), respectively were established through long-term, repeated treatment *in vivo*. Right Panels, Top: Western Blot characterization of RAS pathway signaling in parental and RMC-7977 Resistant HPAF-II tumors. Bottom: representative images of IHC staining of HER2 in Capan-1 parental and daraxonrasib-resistant tumors harvested at 4h post-dosing of vehicle control or daraxonrasib on day 7, shown at 800x magnification. ** p<0.01, *** p<0.001, two-way ANOVA (repeat measures) compared to control

Potential Combination Approaches

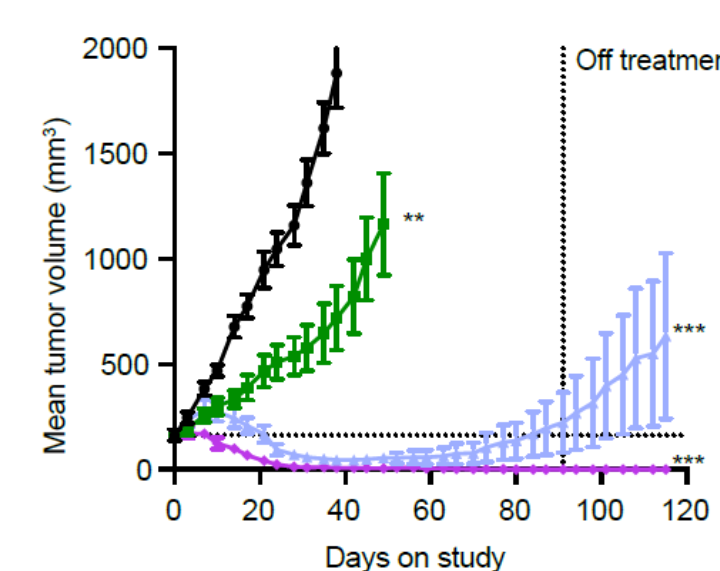
Potential Combination Options: RAS(ON) Mutant-Selective Inhibitors, RTK Inhibitors



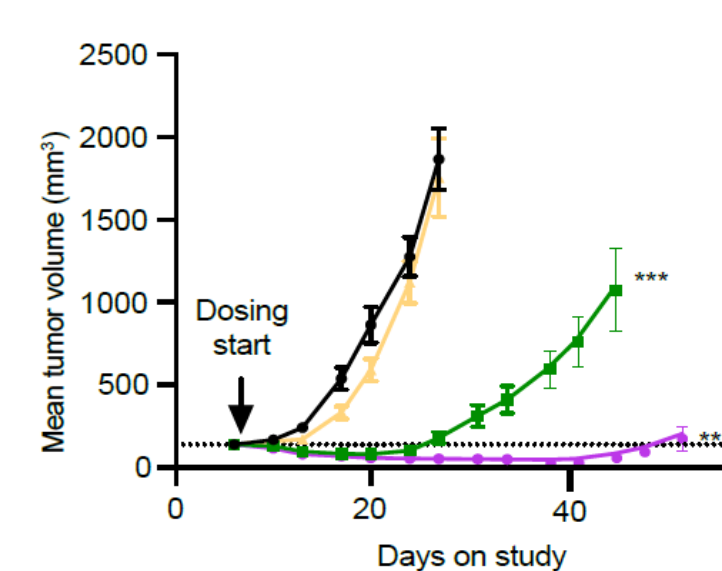
Targeting RAS Signaling Via Combination of Daraxonrasib with HER2 or c-MET and EGFR Inactivation

Daraxonrasib Combined with T-DXd or Amivantamab Led to Deep and Durable Tumor Responses

A. Daraxonrasib Resistant Capan-1 Model



B. KP-4 Model (PDAC, KRAS^{G12D} WT)

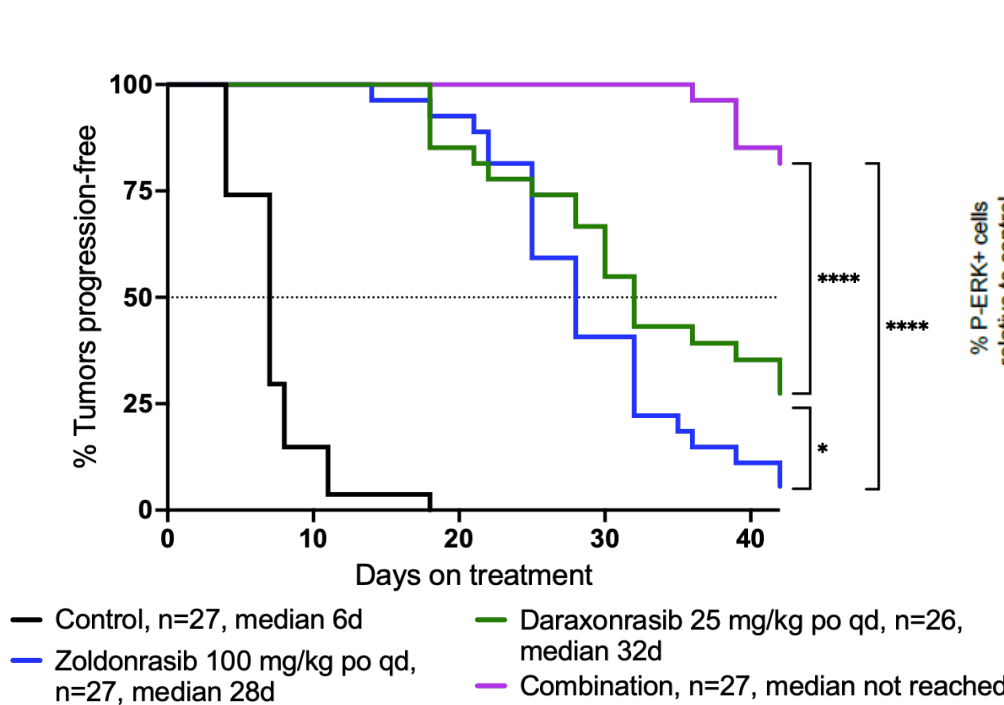


Mean tumor volumes of each group were plotted across the course of treatment (mean ± SEM). A. Mice bearing daraxonrasib-resistant Capan-1 CDX tumors (n=6 per group) were treated with vehicle control, daraxonrasib at 25 mg/kg po qd, T-DXd intravenously (iv) at 4 mg/kg per week, or the combination. B. Mice bearing KP-4 CDX tumors (n=9 per group) were administered with vehicle control, daraxonrasib at 25 mg/kg po qd, amivantamab intraperitoneally (ip) at 10 mg/kg, twice per week (biw), or the combination. ** p<0.01, *** p<0.001, two-way ANOVA (repeat measures) compared to control

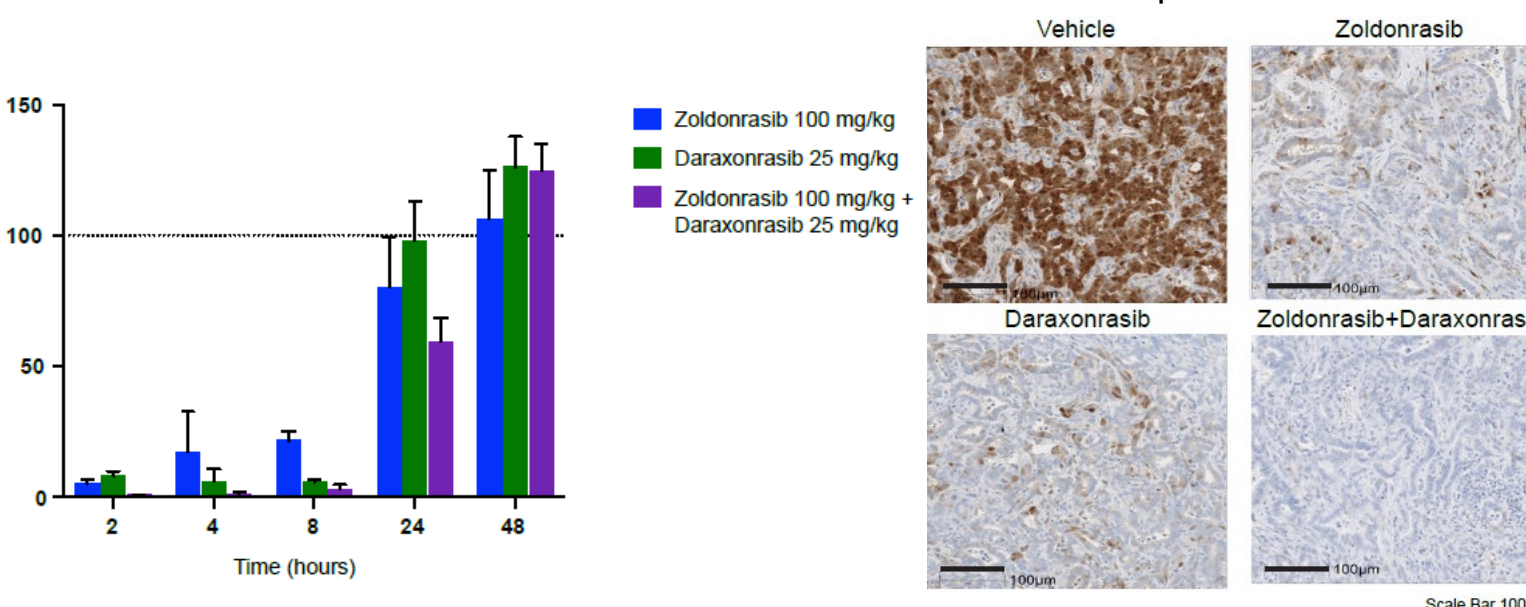
Mitigation of Increased RAS Signaling by RAS(ON) Inhibitor Doublets

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

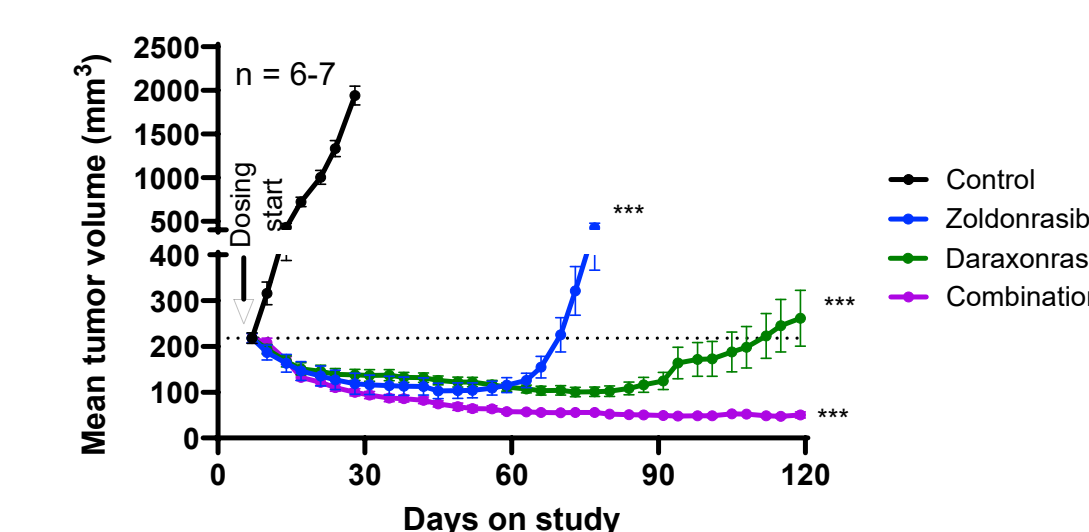
A. RAS(ON) Inhibitor Doublet Increases Progression-free Survival Benefit in KRAS G12D Allograft Models



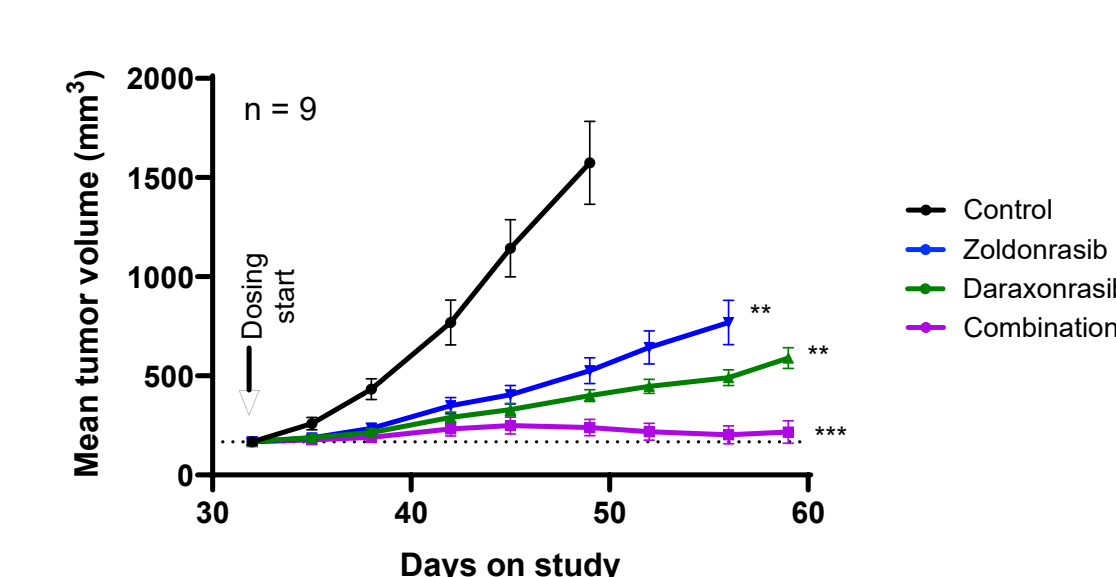
B. RAS(ON) Inhibitor Doublet Further Inhibits Pathway Signaling in KPCyC3 (Kras^{G12D}+/+, Trp53^{R172H})



C. RAS(ON) Inhibitor Doublets in HPAF-II (PDAC, KRAS^{G12D} Amp) Parental Model



D. RAS(ON) Inhibitor Doublets in RMC-7977-Resistant HPAF-II Model



A. Three KPCyC (Kras^{G12D}+/+, Trp53^{R172H}) models: KPCyC3 (2838c3), c4 (6499c4), and c5 (6419c5) derived as described in Li et al.⁸ 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. C&D. Mean tumor volumes of each group were plotted across the course of treatment (mean ± SEM) in the HPAF-II parental or RMC-7977 resistant HPAF-II model. Zoldonrasib dosed at 100 mg/kg po qd; daraxonrasib at 25 mg/kg po qd; zoldonrasib 100 mg/kg po qd + daraxonrasib 10 mg/kg po qd in the combination. ** p<0.01, *** p<0.001, two-way ANOVA (repeat measures) compared to control



Abbreviations: RMC-7977, RAS(ON) multi-selective tool compound; BCA, bicinchoninic acid; CDX, cell line-derived xenograft; CI, confidence interval; CNV, copy number variant; ctDNA, circulating tumor DNA; CTG, Champions TumorGraft; ddPCR, droplet digital PCR; DMSO, dimethyl sulfoxide; DOX, doxycycline; p-ERK, phosphorylated extracellular signal-regulated kinase; gDNA, genomic DNA; 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, non-small cell lung cancer; NSCLC, non-small cell lung cancer; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; 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; T-DXd, trastuzumab deruxetecan; VAF, variant allele frequency; VUS, variant of uncertain significance

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Revolution Medicines Research and Development Teams

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