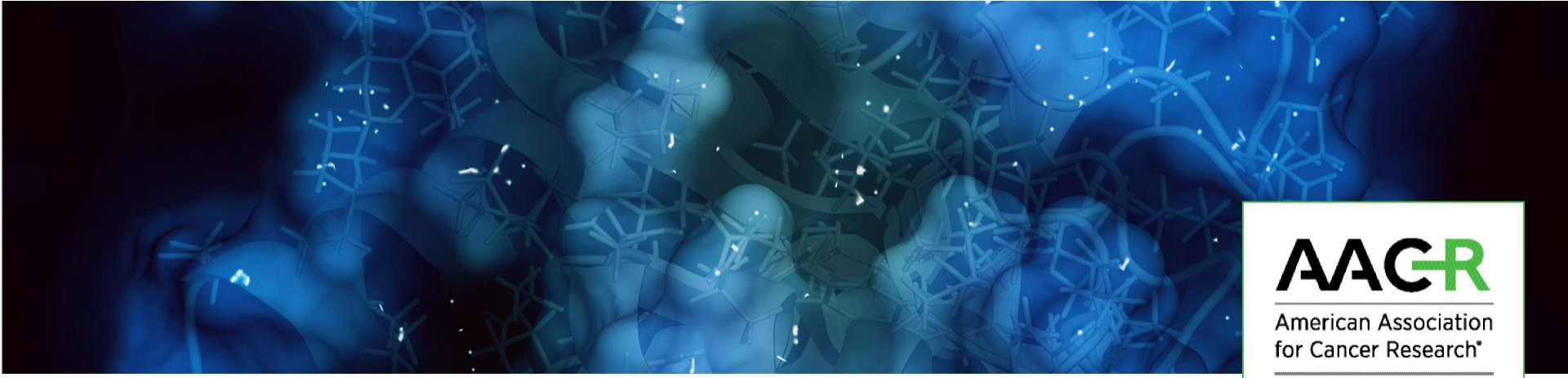


The RAS(ON) Multi-Selective Inhibitor, Daraxonrasib (RMC-6236), Induces Receptor Tyrosine Kinase (RTK) Cell Surface Expression in Pancreatic Cancer Preclinical Models, Providing Rationale for Combinations with RTK Targeting Agents

Yongxian Zhuang, Mark Labrecque, Helena Kiefel, Sumit Kar, Vidya Seshadri, Lingyan Jiang, Xing Wei, Ciara Helland, Yu Chi Yang, Jacqueline A. M. Smith, Jingjing Jiang, Mark Merchant, Mallika Singh and Ida Aronchik.

Revolution Medicines, Redwood City, CA.

RAS ONCOGENESIS AND THERAPEUTICS

March 5-8, 2026 | J.W. Marriott Los Angeles L.A. Live | Los Angeles, CA

Disclosure Information

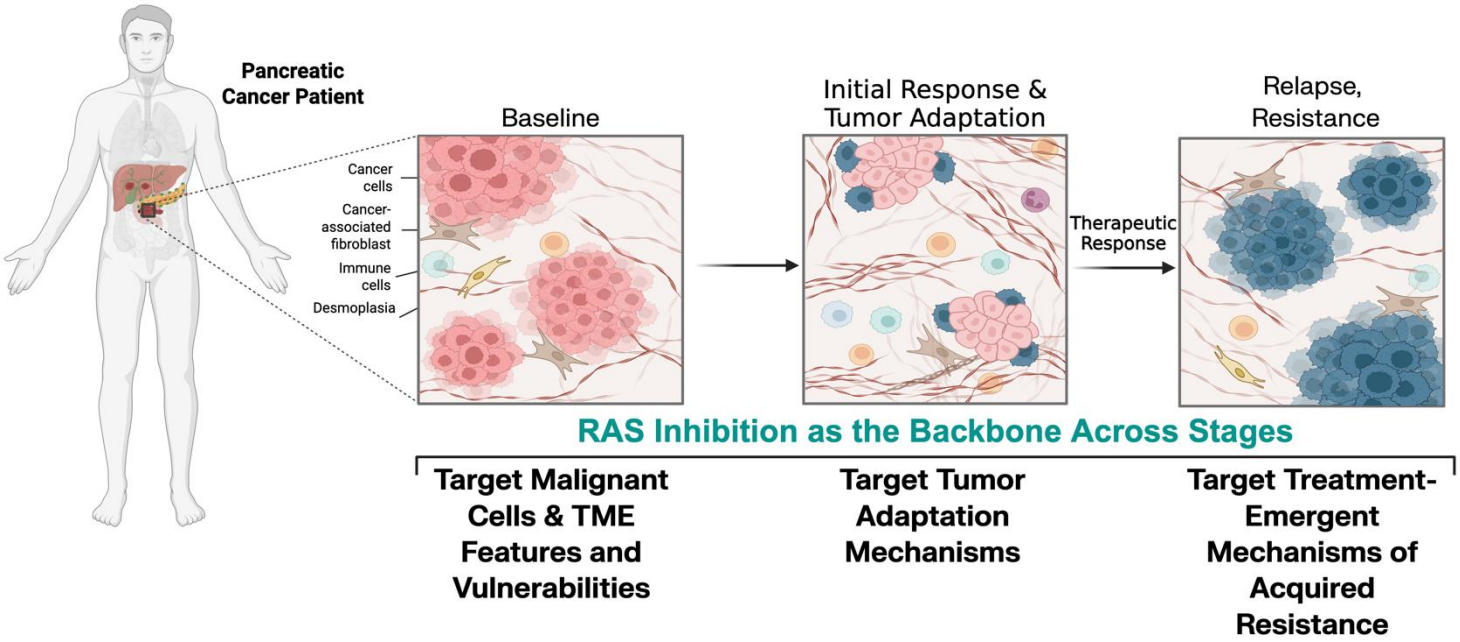
Ida Aronchik, PhD

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

Key Combination Opportunities for Treating RAS-Driven Cancers



Each stage of the treatment journey represents different and overlapping combination opportunities

Targeting concepts courtesy of Andy Aguirre

Figure created in BioRender

Daraxonrasib Resistance in the Clinic Converges on RAS Pathway Activation

- Acquired resistance to RAS/MAPK inhibition converges on pathway reactivation
- A common feature of escape to RAS pathway inhibition is Receptor Tyrosine Kinase (RTK) activation by genomic and post-translational events as well as relief of feedback inhibition
- We observed multiple RTK activating alterations in ctDNA of patients with PDAC who progressed on 160-300 mg daraxonrasib after PFS > 3 months[1]
- Here use preclinical models to characterize potential non-genomic RTK activation events that occur during and after daraxonrasib treatment

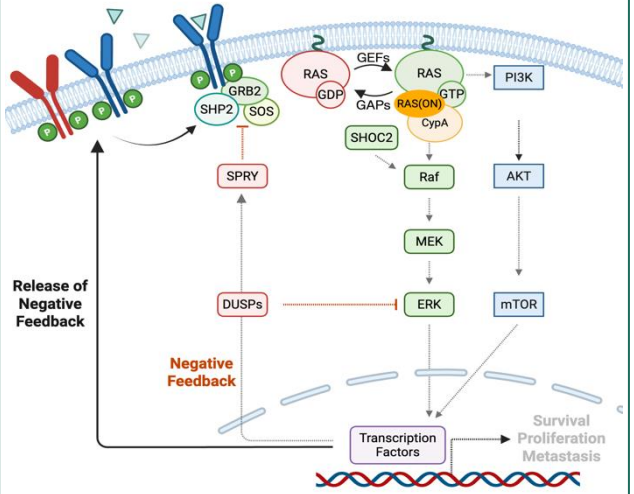
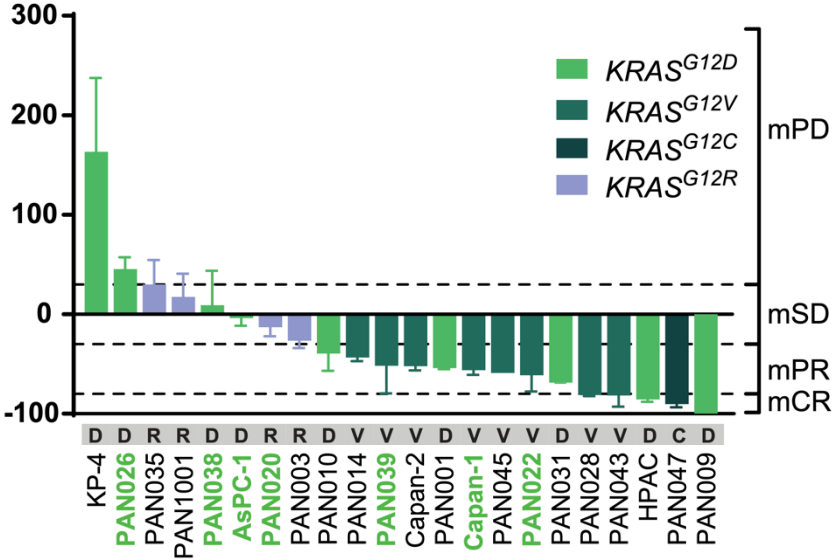


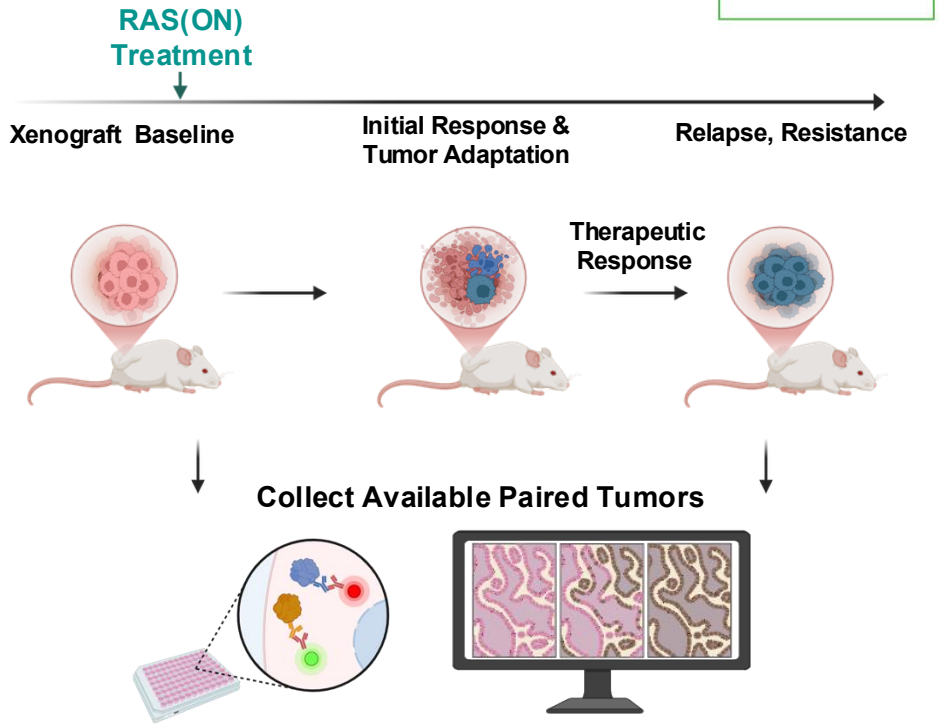
Figure created in BioRender

[1]Adapted from Aronchik, Kar, ENA 2025

Analysis of Daraxonrasib-treated PDAC Preclinical Models To Identify RTK Targets for Combinations



Models with paired EOT samples (in green) were analyzed via IHC

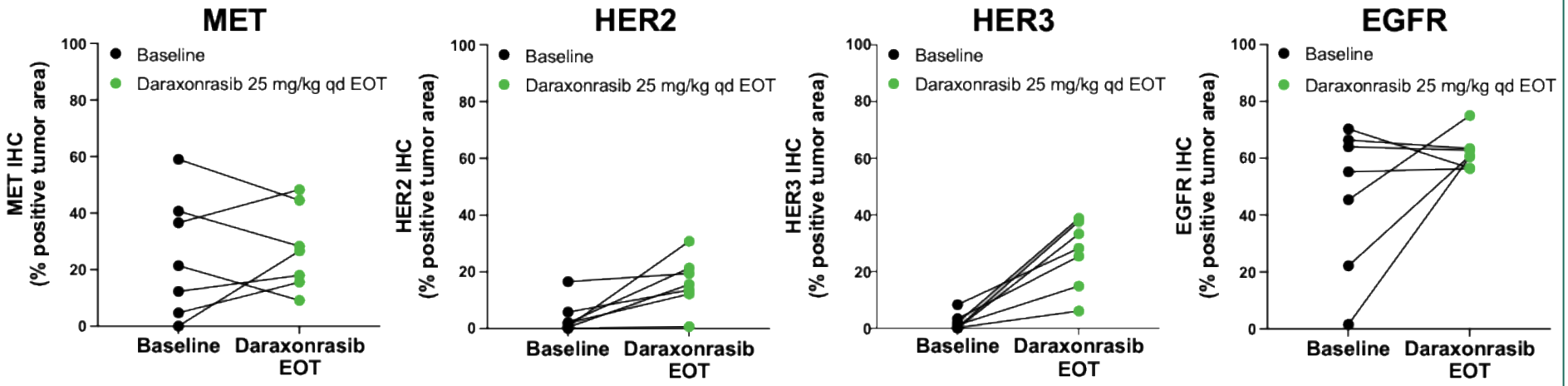


Adapted from Jiang J. et.al. Cancer Discov. 2024 Jun 3;14(6):994-1017.

Created with Biorender

Daraxonrasib Treatment Impacts The Expression of Multiple Receptor Tyrosine Kinases on PDAC Xenograft Tumors

Cell Surface RTK Expression in Xenograft Models Before and After Daraxonrasib Treatment



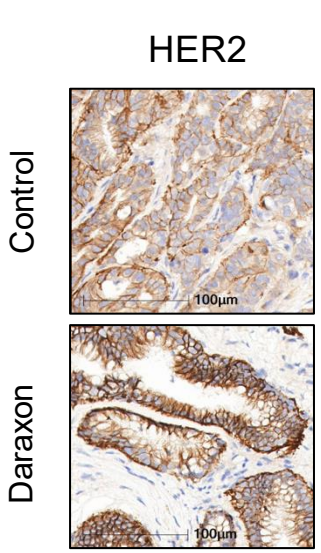
Maintained | Increased | Increased | Increased or Maintained

Paired baseline (**black**; each dot represents a model; n=1 tumor per model) and daraxonrasib end-of-treatment tumors (**green**; each dot represents a model; n=1-3 individual tumors per model)

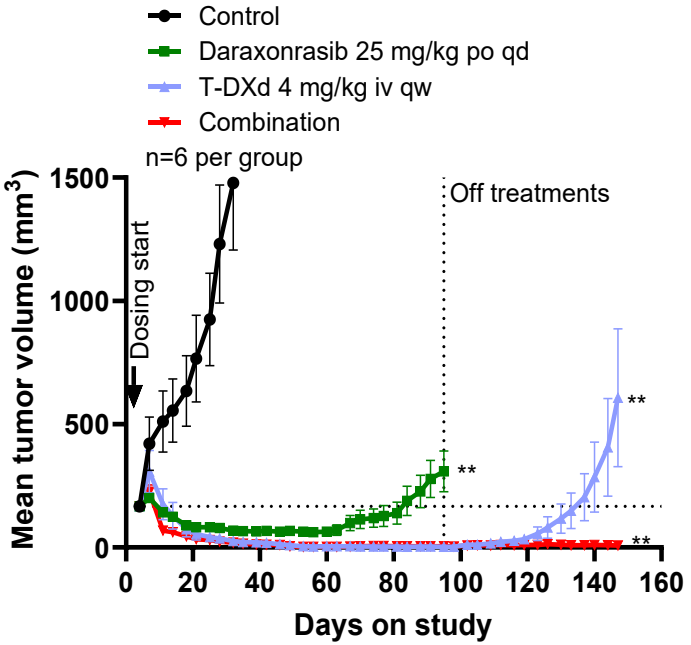
RAS(ON) Inhibition in Combination with Trastuzumab Deruxtecan (T-DXd) in the Treatment-Naïve Setting

AACR American Association for Cancer Research®

Capan-1 (PDAC, *KRAS*$^{G12V/12V}$)



4h post-last dose
on day 7

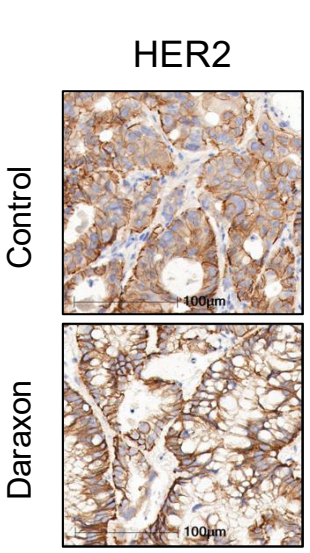


**P < 0.01, control and treatment groups were compared by two-way RM ANOVA on the last day of the control

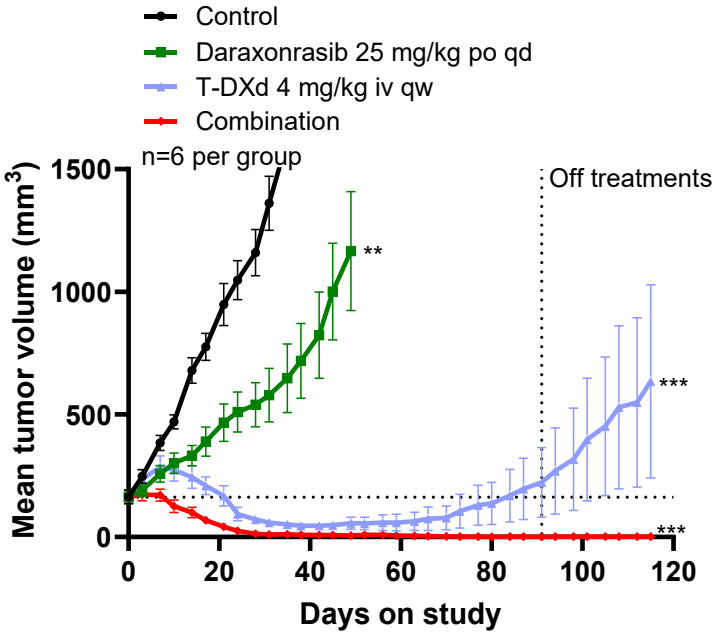
RAS(ON) Inhibition in Combination with T-DXd in the Resistant Setting

AACR
American Association for Cancer Research

Daraxonrasib Resistant Capan-1



4h post-last dose on day 7

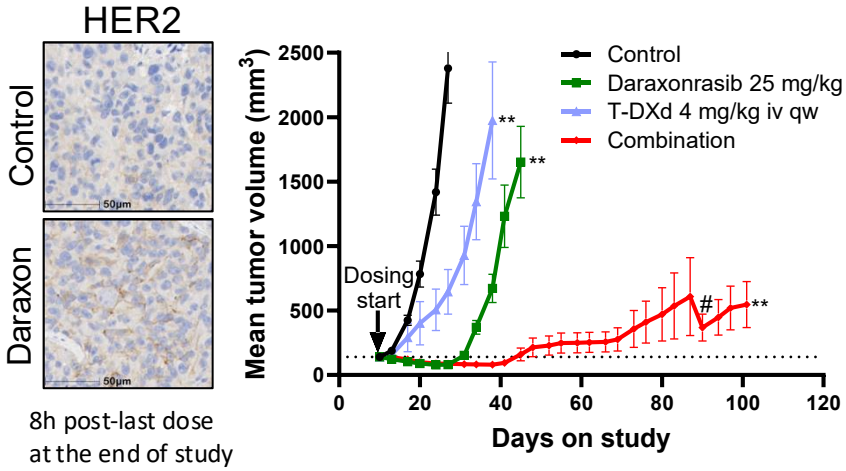


**P < 0.01, ***P < 0.001, control and treatment groups were compared by two-way RM ANOVA on the last day of the control

RAS(ON) Inhibition Combines Effectively With Multiple RTK-Targeted ADCs in a High-Bar PDAC Model

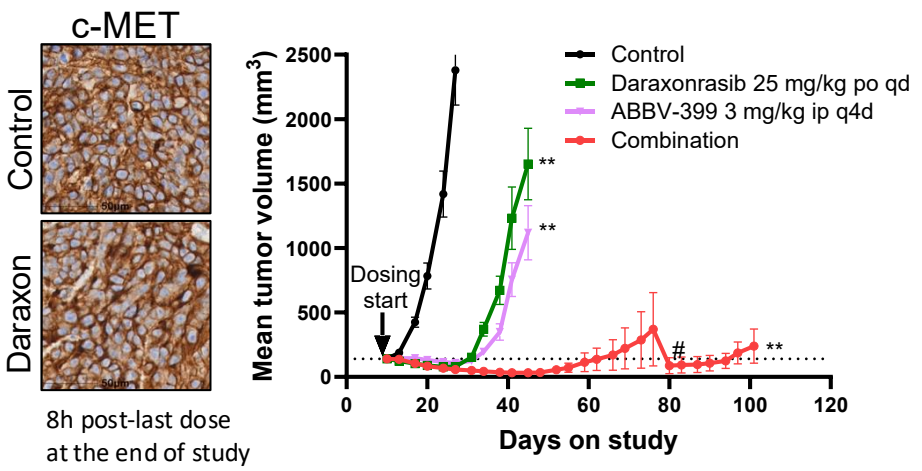
KP-4 (PDAC, *KRAS*$^{G12D/WT}$, *MYC* Amp, c-Met^{+}, HGF^{+})

Daraxonrasib + T-DXd



8h post-last dose at the end of study

Daraxonrasib + ABBV-399 (c-Met-targeting ADC)

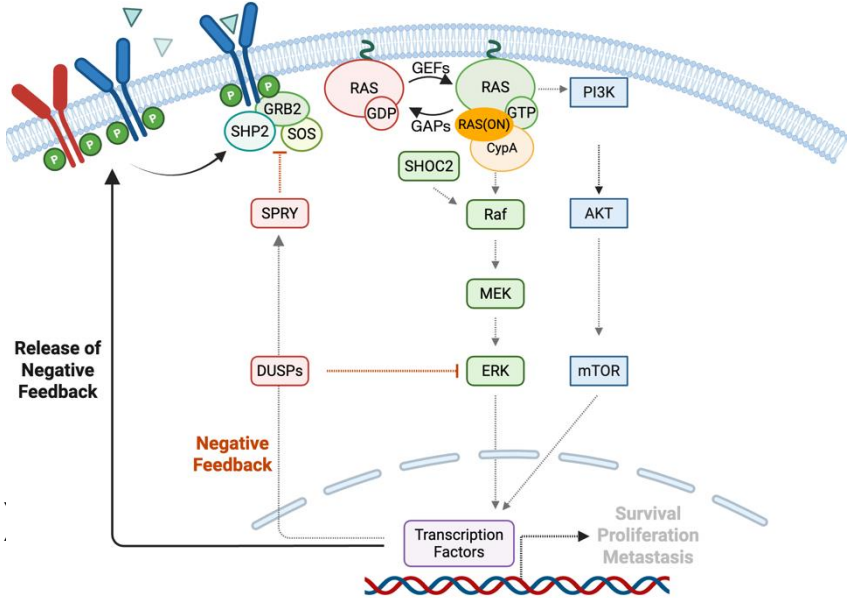


8h post-last dose at the end of study

**P < 0.01, control and treatment groups were compared by two-way RM ANOVA on the last day of the control
n=6 per group, unless noted #

Key Messages

- The preclinical data recapitulate the clinical observation of RAS pathway reactivation observed in ctDNA of daraxonrasib-treated patients with PDAC, progressing after PFS >3 months
- Daraxonrasib treatment is frequently associated with maintenance or upregulation of multiple RTKs (HER2, HER3, MET, etc.) across preclinical tumor models
- RAS(ON) inhibitor combinations with ADCs targeting HER2 or MET enable deeper and more durable antitumor activity in preclinical models
- Ongoing work seeks to define the specific attributes of RTKs that best enable ADC combinations with RAS(ON) inhibition



Created with Biorender

Acknowledgements

- We thank all patients who participated in this study, their families who supported them, and the clinical investigators and research staff who cared for them
- Academic collaborator Kian-Huat Lim
- Revolution Medicines Research and Development Teams

Poster A007

Session: Friday, March 6th