RMC-9805, a First-in-Class, Mutant-Selective, Covalent and Orally Bioavailable KRAS^{G12D}(ON) Inhibitor, Promotes Cancer-Associated Neoantigen Recognition and Synergizes with Immunotherapy in Preclinical Models

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REVOLUTION MEDICINES

Disclosure Information

Marie Menard

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

RMC-9805 is a Mutant-Selective, Covalent, Tri-Complex Inhibitor Targeting KRAS^{G12D}(ON)

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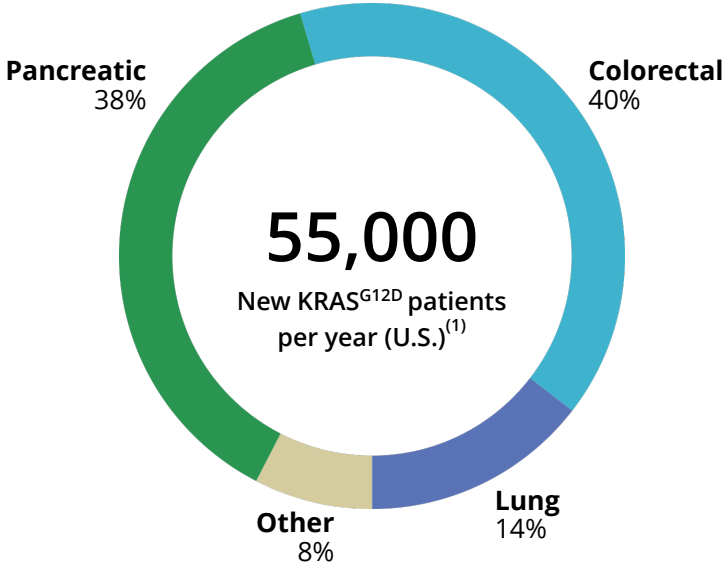

Highly Potent and Selective RAS(ON) Inhibitor

- Highly active against KRAS^{G12D}
- Covalent for irreversible inhibition

Attractive PK/ADME Profile

- Favorable *in vivo* oral bioavailability and clearance for effective target coverage in KRAS^{G12D}-addicted cancer cells

(1) Calculated using tumor mutation frequencies from Foundation Medicine Insights August 2020 and scaled to estimated patient numbers using cancer incidence from ACS *Cancer Facts and Figures* 2020 (see appendix for additional detail); lung cancer = non-small cell lung cancer

Characterization above is based on RVMD preclinical research

RMC-9805 Shows Robust Anti-Tumor Activity *in Vivo* Across Diverse KRAS^{G12D} Xenograft Models

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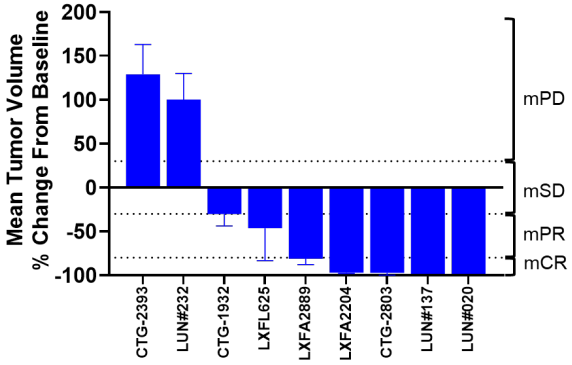
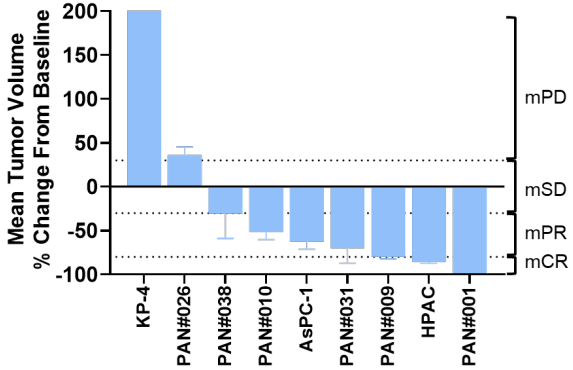
NSCLC

67% ORR (6/9)
78% DCR (7/9)



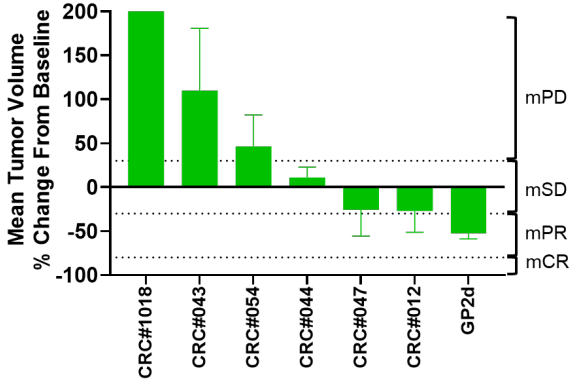
PDAC

78% ORR (7/9)
78% DCR (7/9)



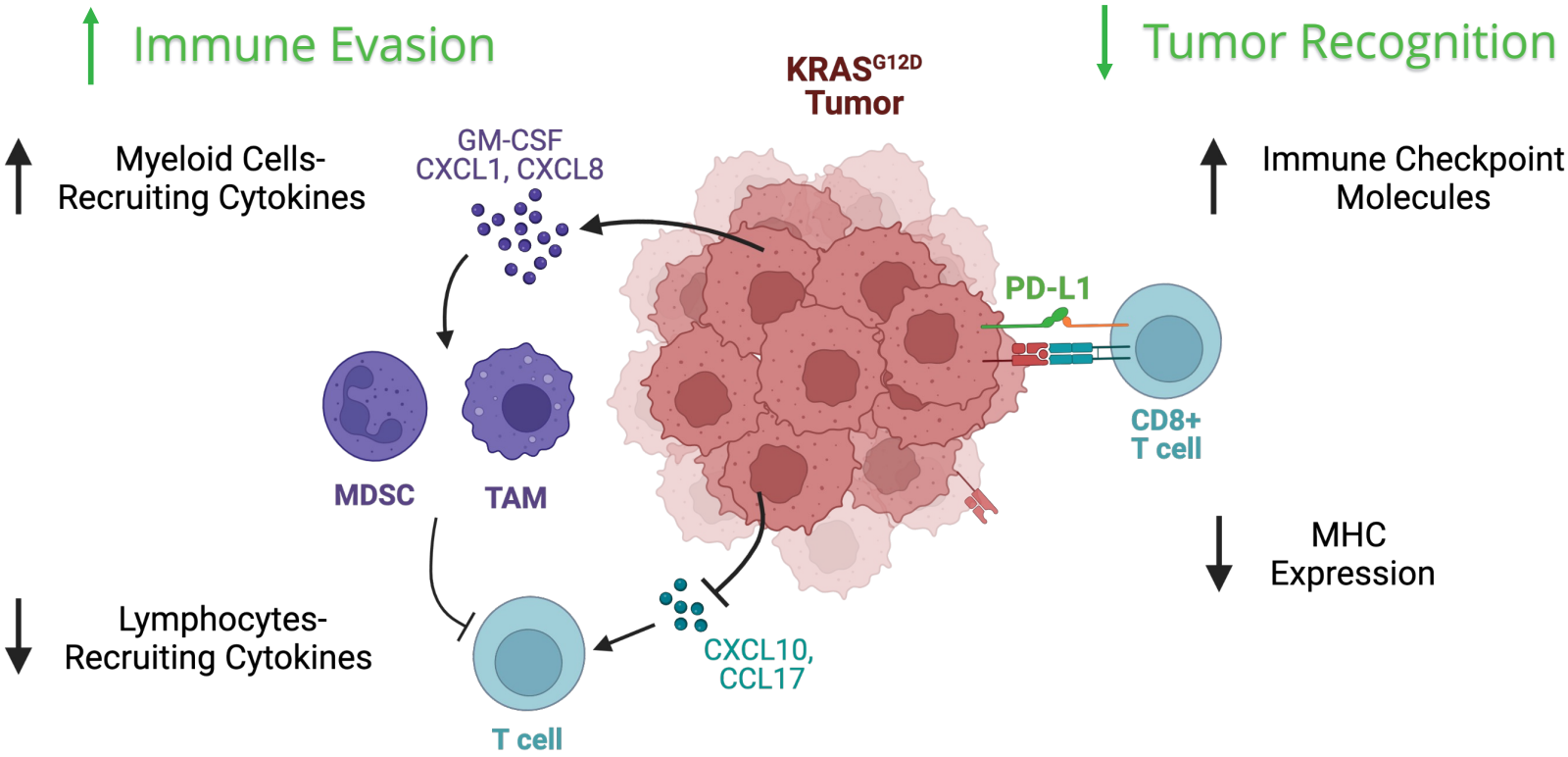
CRC

14% ORR (1/7)
57% DCR (4/7)



RVMD preclinical research as of 11/02/22
RMC-9805 dosed at 100 mg/kg po qd; n=2-8/group
NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma; CRC = colorectal cancer
Responses assigned according to mRECIST (see appendix)
ORR = objective response rate; DCR = disease control rate

Oncogenic RAS Signaling is a Major Driver of Immune Escape in the Tumor



RMC-9805 Reverts Immune Evasive Mechanisms and Sensitizes KRAS^{G12D} Cancer Cells to Immune Attack

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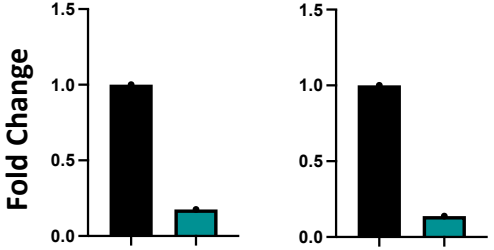
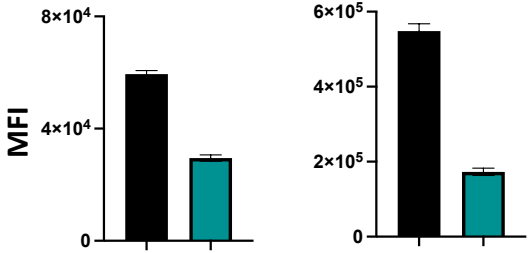
Murine KRAS^{G12D} Cells *In Vitro*

DMSO
RMC-9805

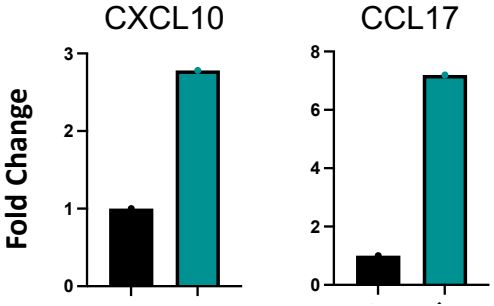
Suppressive Myeloid Cells Factors



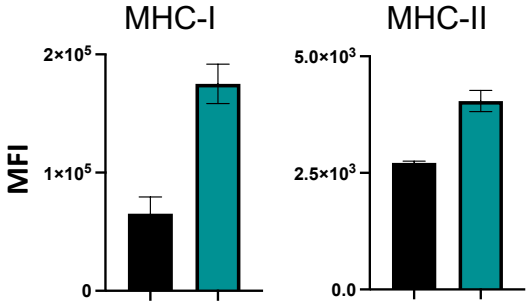
Immune Checkpoint



Lymphocytes-Recruiting Factors



MHC Expression



eCT26 (KRAS$^{G12D/G12D}$) cells or KPCY 6499c4 (KRAS$^{G12D/+}$) cells* treated *in vitro* for 48h with 10nM (left panels) or 100nM (right panel) of RMC-9805
Cytokine levels measured by cytokine array
Cell surface expression measured by flow cytometry

KRAS^{G12D}(ON) Inhibition in Cancer Cells Transforms the TME in Favor of Anti-Tumor Immunity

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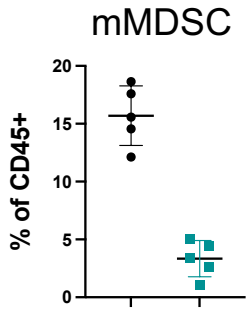
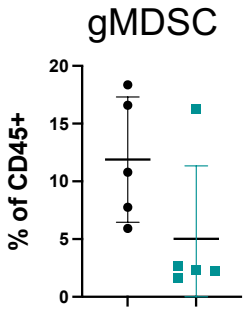
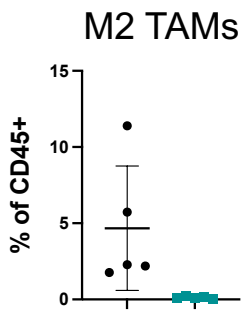
KRAS^{G12D} Syngeneic *In Vivo* Model

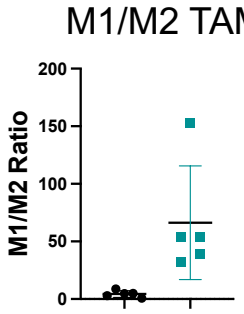
- Vehicle
- RMC-9805 100 mg/kg QD PO

Suppressive Myeloid Cells

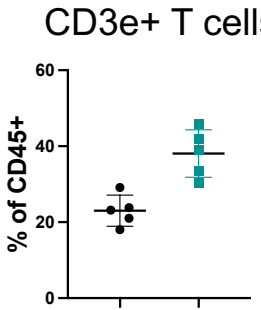


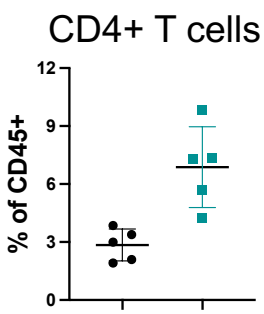


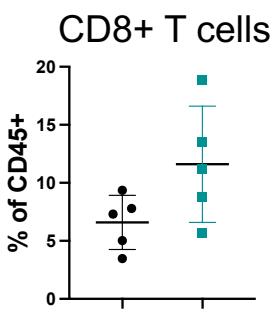




Cytotoxic T Cells







eCT26 (KRAS$^{G12D/G12D}$) tumors treated for 4-8 days *in vivo* and analyzed by flow cytometry 24h after last dose

KRAS^{G12D}(ON) Inhibition Increases Antigen Presentation and TCR Repertoire Diversity *in Vivo*

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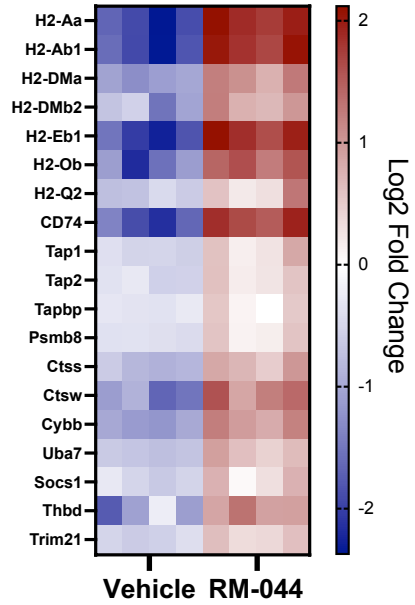
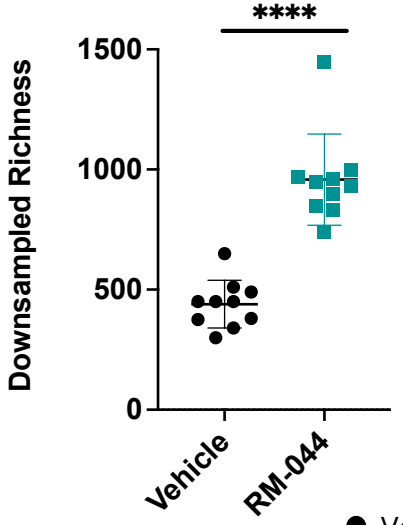
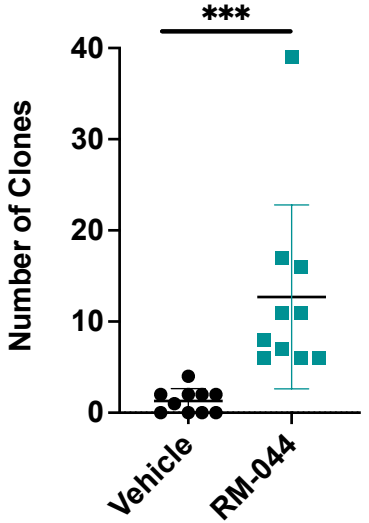
Antigen Processing and Presentation Gene Expression in Tumors



Number of Unique TCR Sequences in Tumors



New, Expanding, Tumor-Associated Clones in Blood



● Vehicle

■ RM-044 = KRAS^{G12D}(ON) inhibitor 100 mg/kg PO QD

eCT26 (KRAS$^{G12D/G12D}$) tumors treated for 4 days with vehicle or RM-044 at 100 mg/kg QD PO - Nanostring IO 360 murine panel on tumors

eCT26 (KRAS$^{G12D/G12D}$) tumor-bearing mice treated for 8 days tumors and blood analyzed by TCR sequencing
***p<0.001 ; **** p<0.0001 post-hoc Dunn test with Bonferroni correction

KRAS^{G12D}(ON) Inhibition Drives Durable Regressions in an Immune Cell-Dependent Manner

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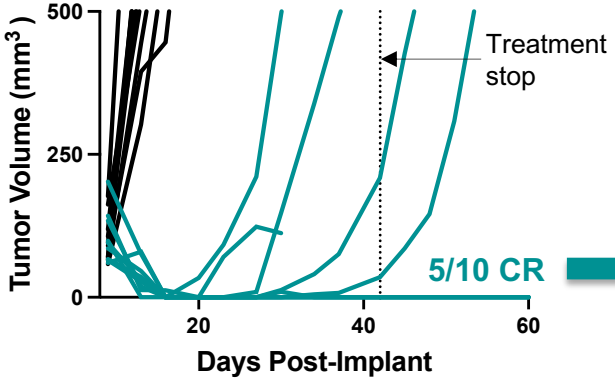
Durable Complete Responses in Immunocompetent Hosts

Balb/c

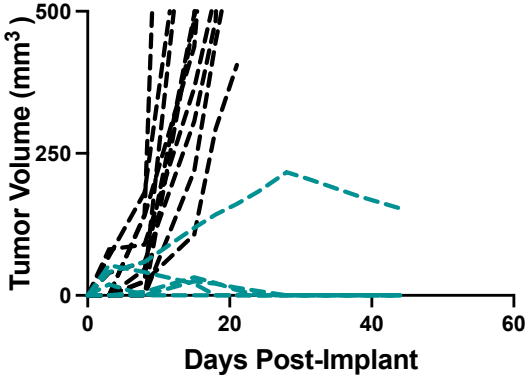


- Vehicle
- RM-044, KRAS^{G12D}(ON) inhibitor 100 mg/kg PO QD

eCT26 (KRAS$^{G12D/G12D}$) tumors treated for 42 days, treatment stop indicated by vertical dashed line

Immunological Memory Demonstrated Upon Rechallenge

Balb/c

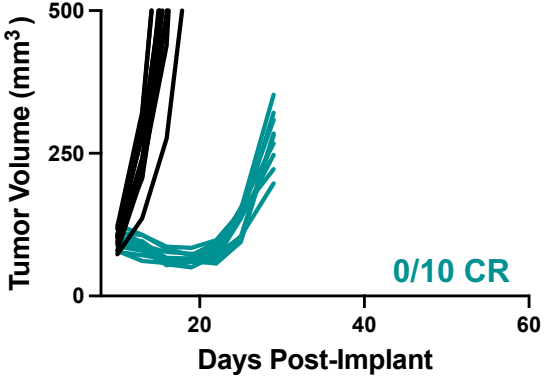


- Naive mice
- Complete responders to KRAS^{G12D}(ON) inhibitor

eCT26 (KRAS$^{G12D/G12D}$) tumors rechallenged 40 days after treatment stopped

No Complete Responses in Immunodeficient Hosts

NSG

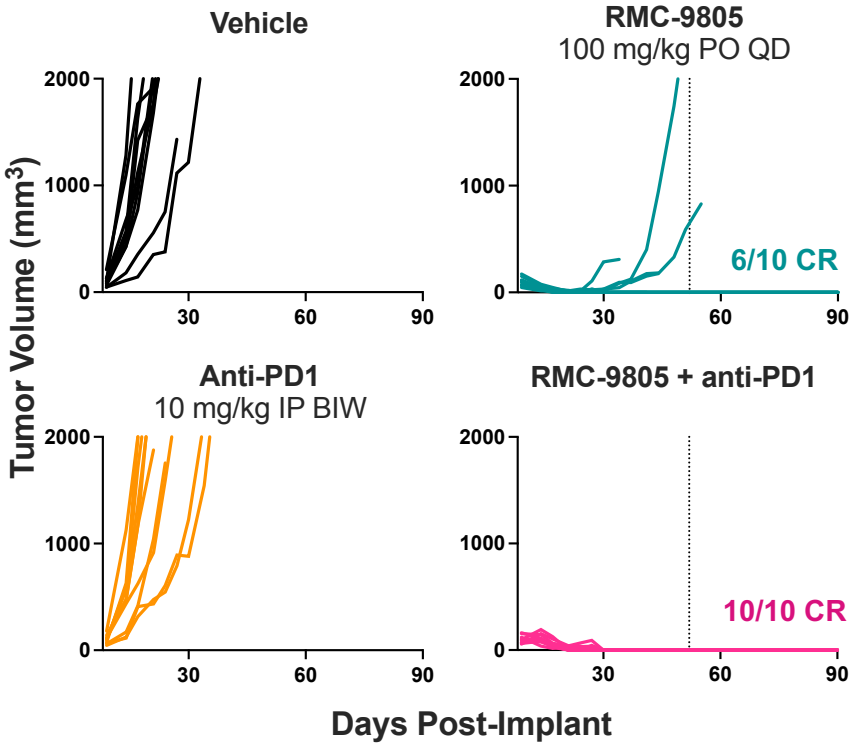


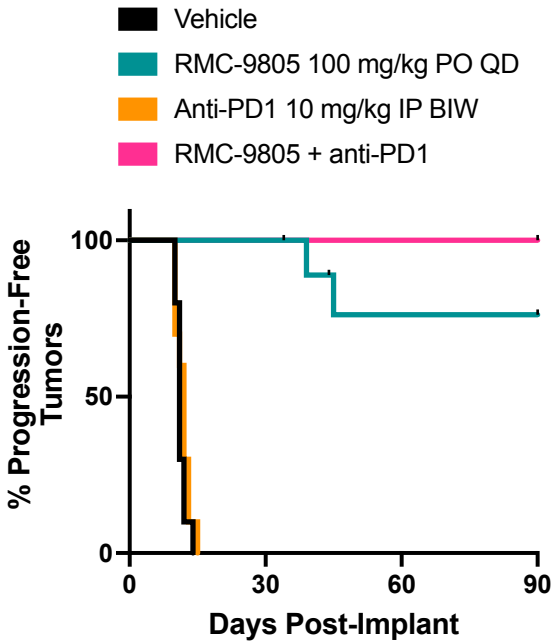
- Vehicle
- RM-044, KRAS^{G12D}(ON) inhibitor 100 mg/kg PO QD

eCT26 (KRAS$^{G12D/G12D}$) tumors treated for 20 days

Combination of RMC-9805 with Anti-PD1 Enhances Durable Complete Responses

Balb/c





eCT26 ($KRAS^{G12D/G12D}$) tumors treated for 42 days, treatment stop indicated by vertical dashed line

RMC-9805 + Anti-PD1 Shows Significant Combination Benefit in an Orthotopic KRAS^{G12D} PDAC Model

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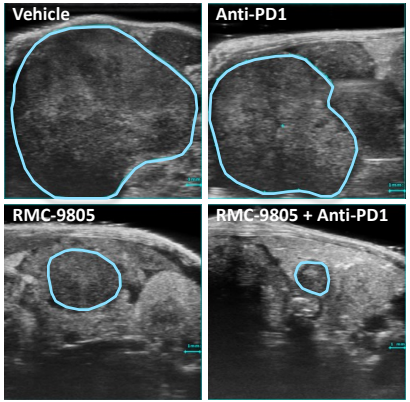
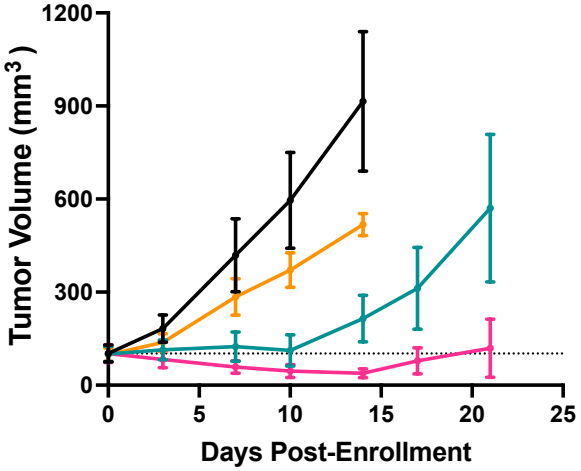
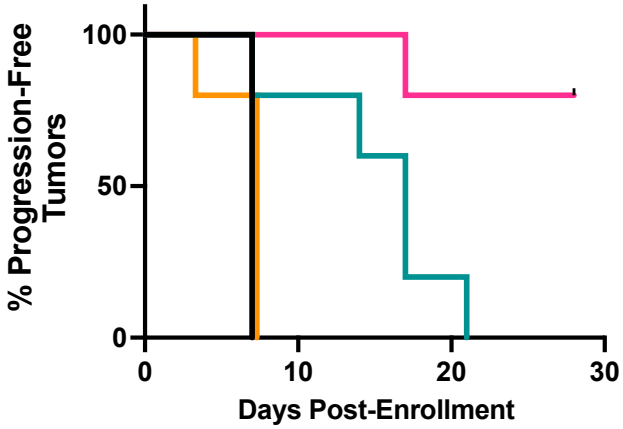
KPCY GEMM-Derived Orthotopic Model

Vehicle
Anti-PD1 10 mg/kg IP BIW
RMC-9805 100 mg/kg PO QD
RMC-9805 + anti-PD1



Representative ultrasound images – treatment day 14





KPCY 2838c3 (KRAS$^{G12D/+}$; p53$^{R172H/+}$) tumors treated for 21 days. Kaplan-Meier progression defined as tumor doubling from baseline

RMC-9805 Creates a Favorable Environment For Combination with Immune-Directed Therapies

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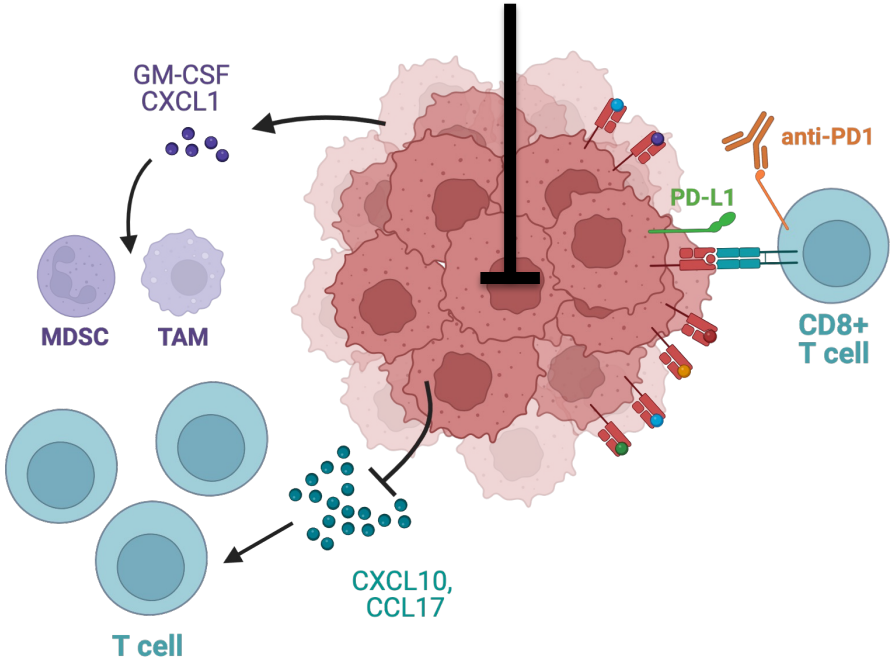
PROMOTES A PERMISSIVE TME

RMC-9805

FAVORS TUMOR RECOGNITION

↓ **Immunosuppressive Myeloid Cells**

↑ **T cell Infiltration**



↑ **MHC Expression and Antigen Presentation**

↓ **Immune Checkpoints**

↑ **TCR Repertoire Diversity**

Acknowledgements

- Revolution Medicines Research and Development Teams

- We thank Ben Z. Stanger, University of Pennsylvania for providing the KPCY GEMM-derived PDAC models