Combination of RAS(ON) Multi-Selective and G12D-Selective Inhibitors Improves Antitumor Activity and Enhances Antitumor Immunity in Preclinical Models of KRAS^{G12D}-Driven Cancers

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Introduction

RAS is one of most common cancer mutations. Oncogenic RAS mutations elevate the levels of active GTP-bound RAS (RAS(ON)). G12D is the most common RAS variant, with 61,000 new patients per year in the US alone, occurs in 40%, 15% and 4% of patients with PDAC, CRC, and NSCLC, respectively[1].

Our investigational agents RMC-9805, a RAS(ON) G12D-selective covalent inhibitor, and RMC-6236, a RAS(ON) multi-selective non-covalent inhibitor of both mutant and wild-type variants of canonical RAS isoforms, exhibit potent antitumor activity as monotherapies in *KRAS^{G12D}* preclinical models[2,3,4].

Reactivation of MAPK pathway has been identified as one of the major mechanisms of clinical resistance (MOR) to KRAS^{G12C}(OFF) mutant-selective inhibitors[5,6]. Similar MOR to a KRAS^{G12D}(OFF) inhibitor were observed in preclinical models[7].

Here present preclinical data that support the hypothesis that a RAS(ON) doublet has the potential to counter some of the common mechanisms of both intrinsic and acquired resistance that may be anticipated in *KRAS^{G12D}* tumors in response to RAS-targeted therapy.

Revolution Medicines Potential Clinical Approaches to Target RAS^{G12D} Mutant Cancers

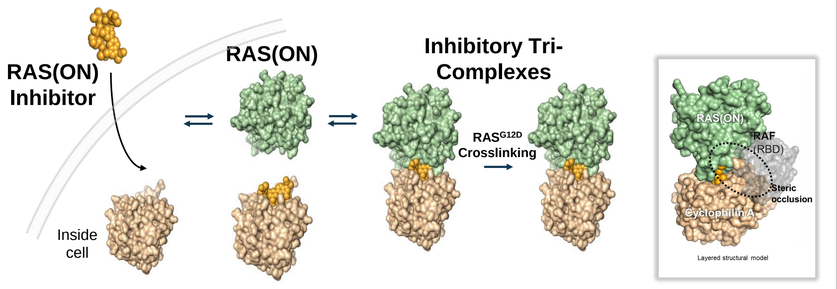
RMC-6236 RAS(ON) Multi-Selective

- Monotherapy with broad potential for RAS-addicted cancers
- Backbone of RAS(ON) inhibitor doublets with mutant-selective RAS(ON) inhibitors
- Targeted agent for SOC combinations, including immunotherapies

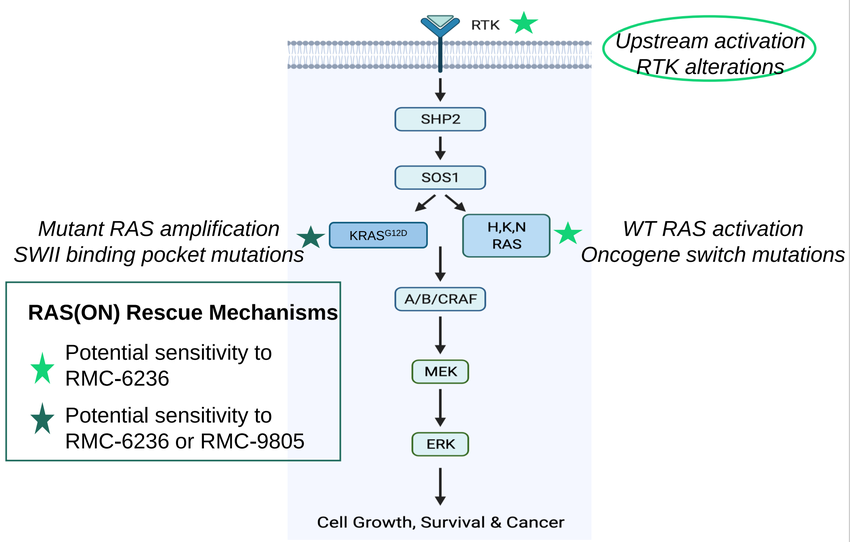
RMC-9805 RAS(ON) G12D-Selective

- Alternative monotherapy approach
- Complementary to RAS multi-selective inhibitor in RAS(ON) inhibitor doublet
- Differentiated targeted agent profile for SOC combinations, including immunotherapies

Mechanism of Action

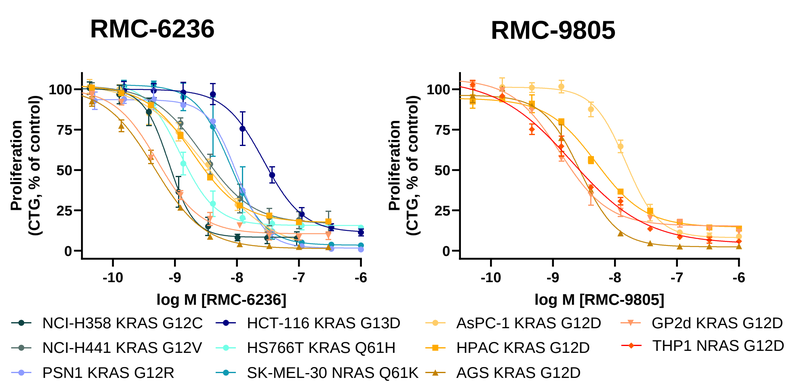


RAS(ON) Inhibitors May Counter Multiple Potential Mechanisms of Resistance to KRAS^{G12D}(OFF) Inhibitors

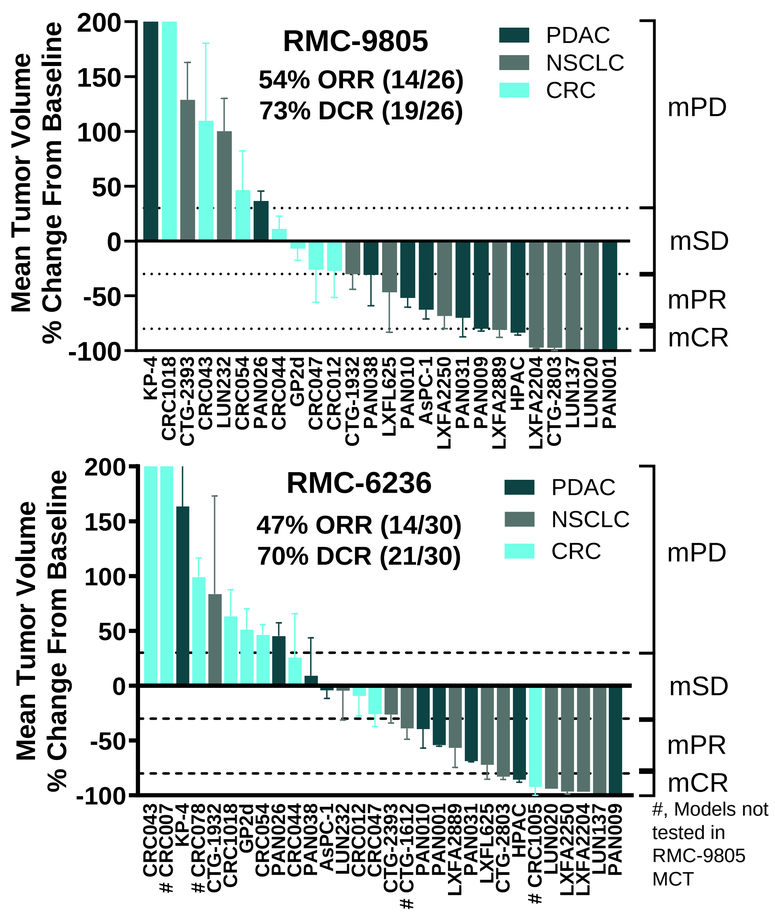


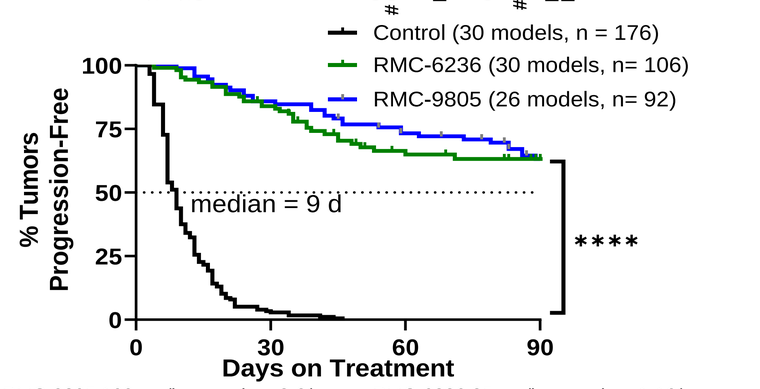
Key Results

Antiproliferative Activity of RMC-6236 and RMC-9805 in RAS Mutant Cancer Cells



Potent & Durable Antitumor Response of RMC-9805 and RMC-6236 in *KRAS^{G12D}* Xenograft Models

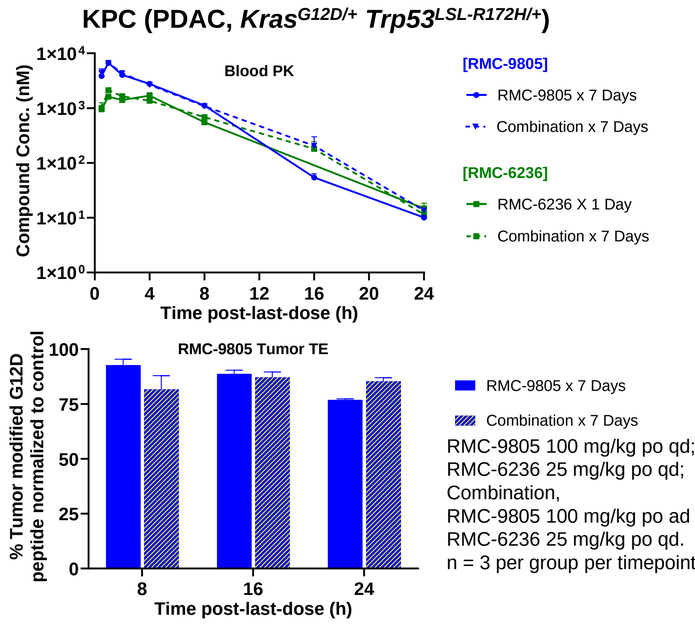




RMC-9805 100 mg/kg po qd, n=2-9/group; RMC-6236 25 mg/kg po qd, n=1-10/group
Responses after 28 ± 2 days of treatment assigned according to mRECIST[8]
Progression defined as tumor doubling from baseline; ****p<0.0001, Log-rank test

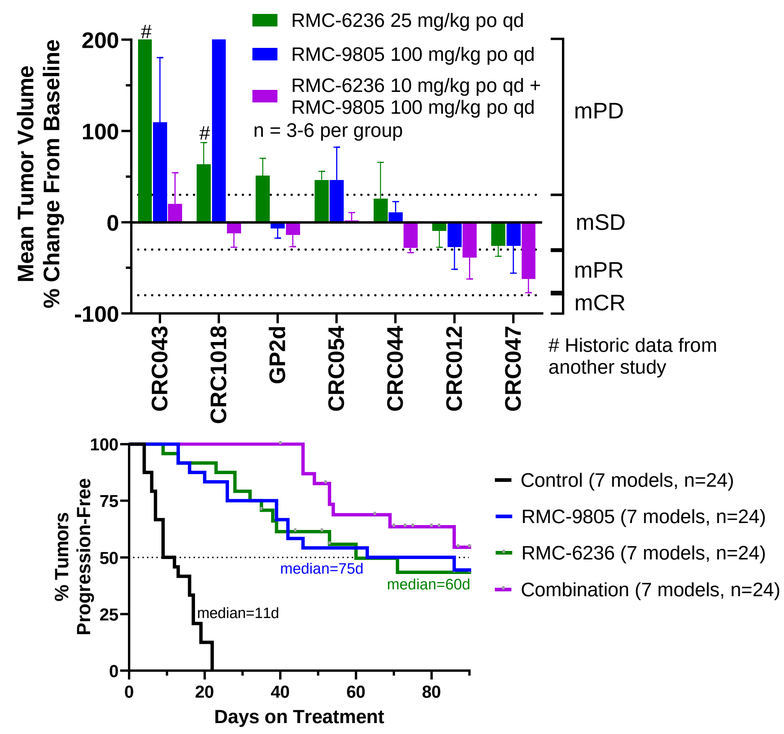
Durable Covalent KRAS^{G12D}Target Engagement (TE) in Tumor with RMC-9805 in Combination with RMC-6236

KPC (PDAC, *Kras$^{G12D/+}$ Trp53$^{LSL-R172H/+}$*)



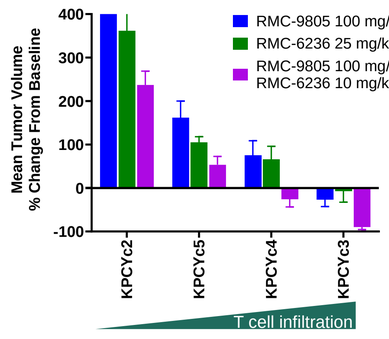
RMC-9805 100 mg/kg po qd;
RMC-6236 25 mg/kg po qd;
Combination,
RMC-9805 100 mg/kg po ad + RMC-6236 25 mg/kg po qd.
n = 3 per group per timepoint.

RMC-6236 + RMC-9805 Improves Depth and Durability of Antitumor Response in *KRAS^{G12D}* CRC Xenograft Models

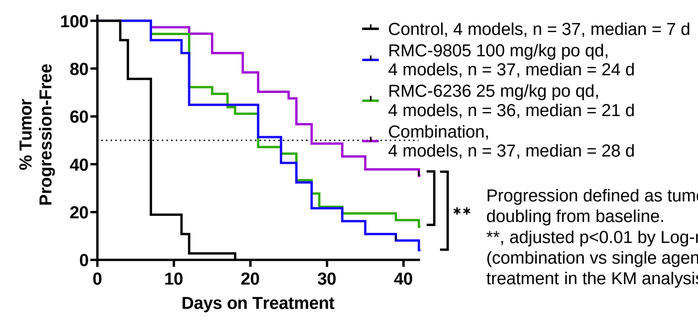


RMC-6236 + RMC-9805 Improves Depth and Durability of Antitumor Response in *Kras^{G12D}* PDAC Allograft Models

KPCY (PDAC, *Kras$^{G12D/+}$ Trp53$^{LSL-R172H/+}$*)

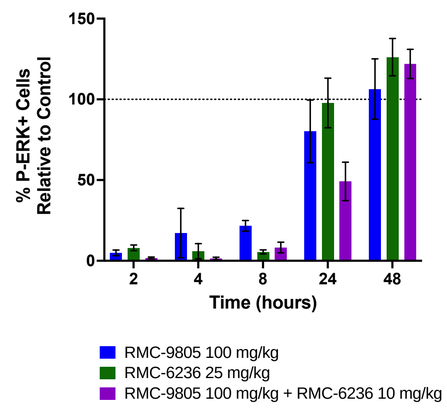


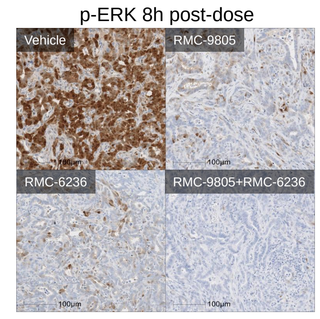
Mice were treated for 42 days; n=7-10/group. All dose regimens were tolerated based on BW assessment. Mean tumor volume change from baseline after 21 days of treatment. KPCY models derived as described in Li et al. Immunity 2018 (Ben Stanger lab, University of Pennsylvania)
T cell infiltration determined by flow cytometry analysis (CD45+ CD3e+) on tumors at baseline



Progression defined as tumor doubling from baseline.
**, adjusted p<0.01 by Log-rank test (combination vs single agent treatment in the KM analysis).

RMC-6236 + RMC-9805 Provides Durable Tumor RAS Pathway Suppression in the KPCYc3 Model

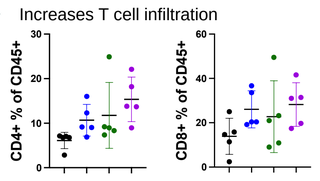




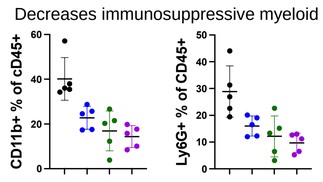
p-ERK signal quantified in panCK+ tumor cells, data represent mean of n=3 tumors per timepoint

RMC-6236 + RMC-9805 Promotes Antitumor Immunity in the KPCYc3 Model

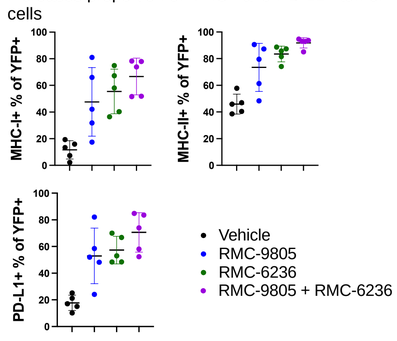
- Increases T cell infiltration



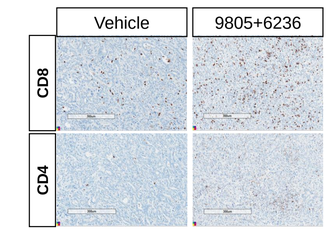
- Decreases immunosuppressive myeloid cells



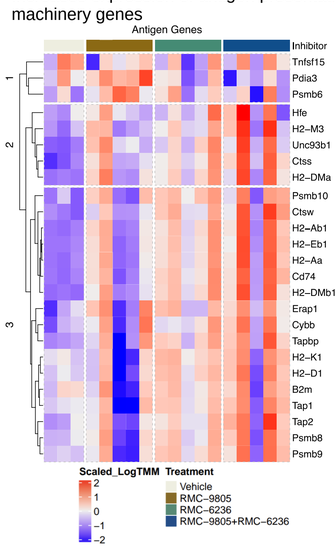
- Increases proportion of MHC+ and PD-L1+ tumor cells



- Increases infiltration of T cells in the core of the tumor



- Increases expression of antigen presentation machinery genes



Tumors dosed for 8 days and analyzed 24h post last dose by flow cytometry, IHC, and nanostring mouse 360 IO panel.

Conclusion

- The investigational agents, RMC-9805, a RAS(ON) G12D-selective inhibitor, and RMC-6236, a RAS(ON) multi-selective inhibitor, exhibited potent antitumor activity as monotherapies in *KRAS^{G12D}* preclinical models
- RMC-6236 + RMC-9805 improved the depth and durability of antitumor response in CRC xenograft models and immunocompetent PDAC allograft models
- In the immunocompetent GEMM-derived PDAC KPCY models, RMC-6236 + RMC-9805
  - led to deeper tumor RAS pathway suppression
  - favored anti-tumor immunity by increasing T cell infiltration and decreasing immunosuppressive myeloid cells, and promoted antigen presentation
- The combination of RMC-6236 and RMC-9805 has the potential to counter some of the intrinsic and acquired resistance mechanisms that may be anticipated in *KRAS^{G12D}* tumors in response to RAS-targeted therapy
- Clinical evaluation of RMC-6236 in combination with RMC-9805 in *KRAS^{G12D}* mutant solid tumors is ongoing (https://clinicaltrials.gov/study/NCT06040541)

References:
(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023
(2) J. Jiang *et al.*, Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov*, OF1-OF24 (2024).
(3) M. Holderfield *et al.*, Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. *Nature* **629**, 919-926 (2024).
(4) U. N. Wasko *et al.*, Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer. *Nature* **629**, 927-936 (2024).
(5) N. Tanaka *et al.*, Clinical Acquired Resistance to KRAS(G12C) Inhibition through a Novel KRAS Switch-II Pocket Mutation and Polyclonal Alterations Converging on RAS-MAPK Reactivation. *Cancer Discov* **11**, 1913-1922 (2021).
(6) M. M. Awad *et al.*, Acquired Resistance to KRAS(G12C) Inhibition in Cancer. *N Engl J Med* **384**, 2382-2393 (2021).
(7) J. Dilly *et al.*, Mechanisms of resistance to oncogenic KRAS inhibition in pancreatic cancer. *Cancer Discov*, (2024).
(8) H. Gao *et al.*, High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nat Med* **21**, 1318-1325 (2015).

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