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Discovery of RMC-9805, an Oral, RAS(ON) G12D-Selective Covalent Tri-Complex Inhibitor

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Revolution Medicines

Disclosure Information

John E. Knox

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

Excessive RAS(ON) Signaling Drives 30% of Human Cancers, Targeted by RAS(ON) Inhibitors

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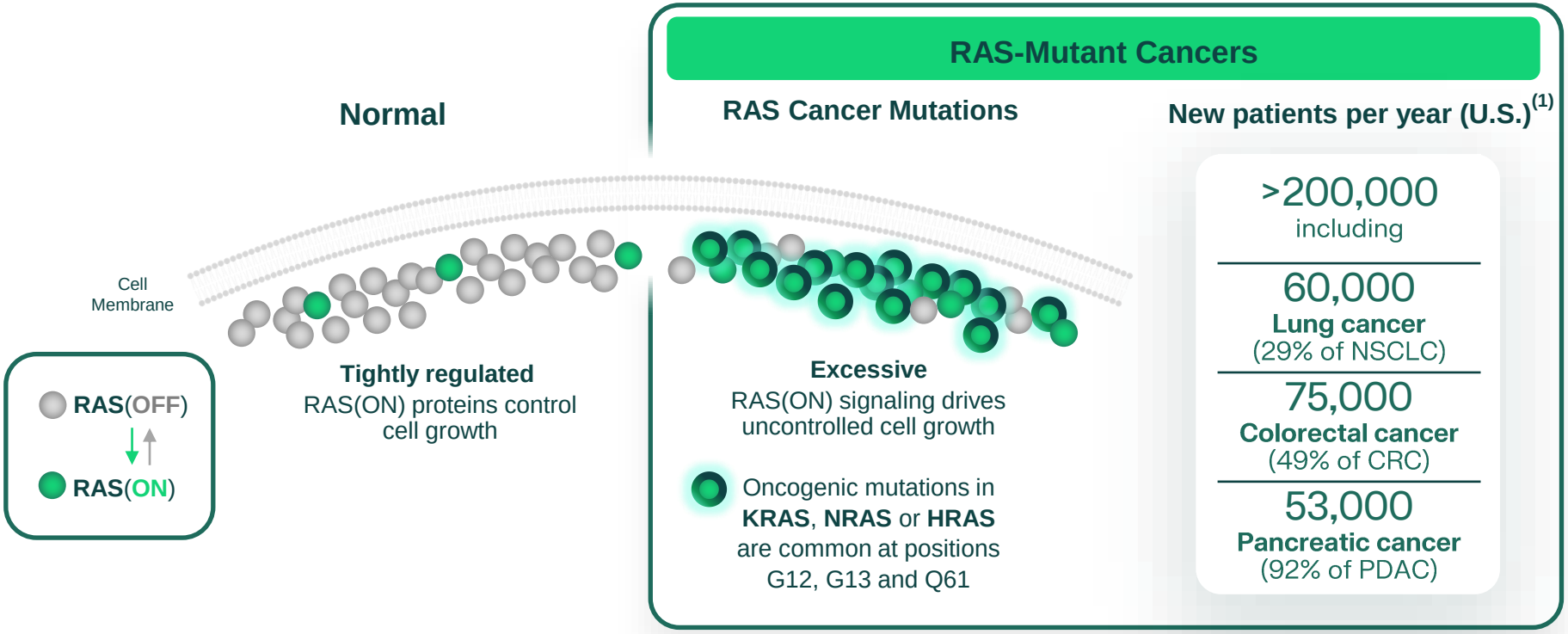

(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023

Multiple Approaches to Targeting KRAS^{G12D} Mutant Cancers - a Large Unmet Medical Need

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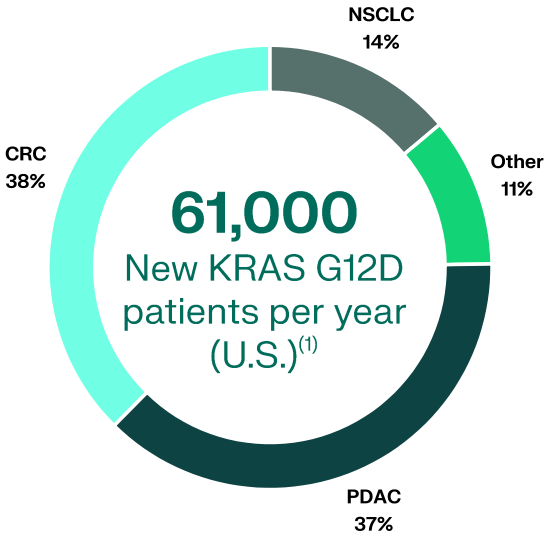
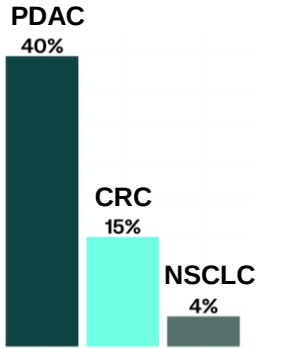
Clinical Unmet Need for KRAS^{G12D}





KRAS^{G12D} Frequency by Tumor Type

Revolution Medicines Clinical Approaches to G12D

RMC-6236
RAS(ON) Multi-Selective*

- Noncovalent, selective inhibitor of mutant and wild-type RAS(ON) proteins
- Targeted agent for SOC combinations, including immunotherapies
- RAS(ON) inhibitor doublet combination

RMC-9805
RAS(ON) G12D-Selective

- Covalent and highly selective for RAS^{G12D}(ON) proteins
- Differentiated targeted agent for SOC combinations, including immunotherapies
- RAS(ON) inhibitor doublet combination

(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

*Koltun et al, **RMC-6236, a RAS(ON) Multi-Selective Tri-Complex Inhibitor**
ADT06: Targeting KRAS beyond G12C
Tuesday, April 9, 2024, 12:30-2:00 pm

Tri-Complex Modality Enables Selective Covalent Targeting of Oncogenic RAS^{G12D}(ON) Proteins

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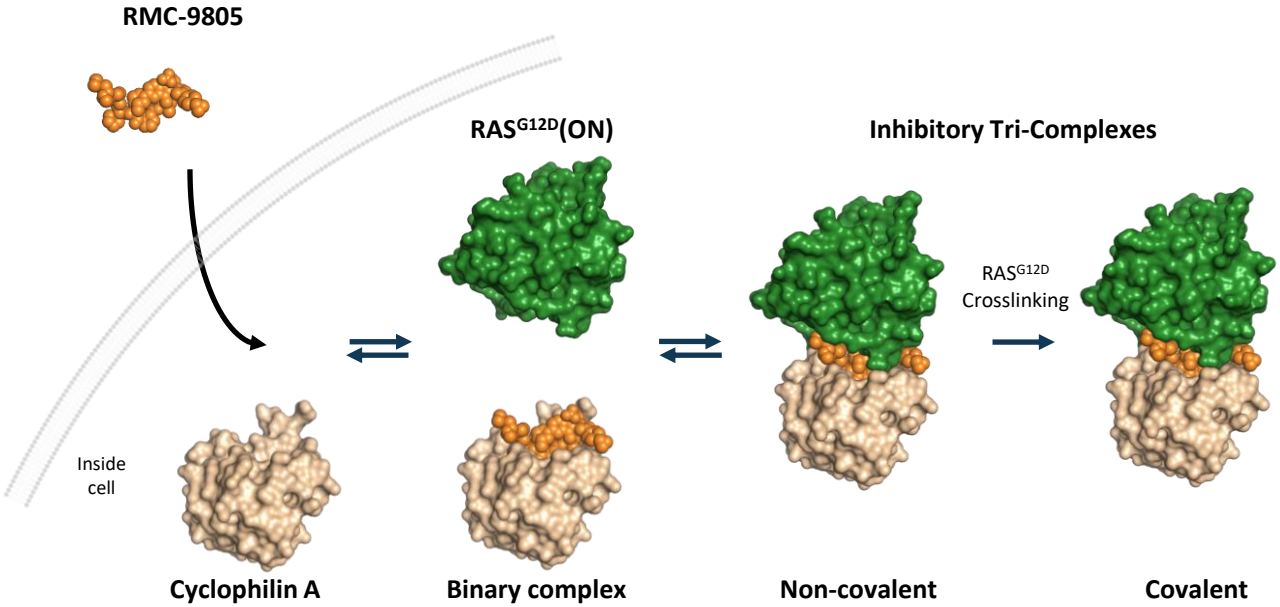
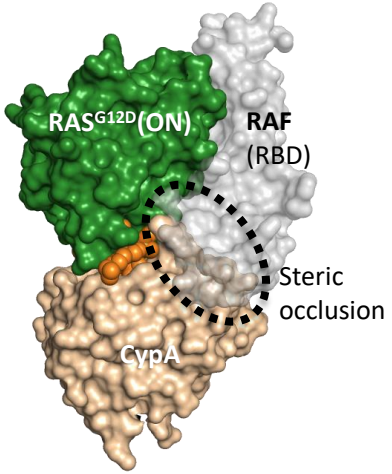


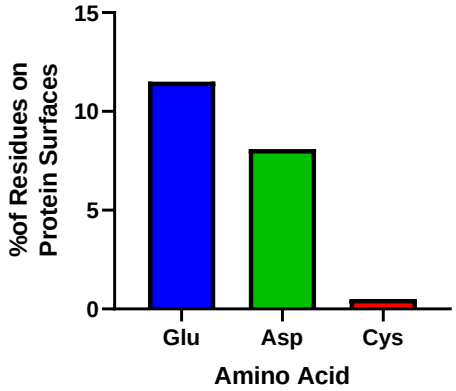


Layered Structural Model

"Chemical leverage of aspartic acid by covalent $KRAS^{G12D}$ inhibitors will likely be impossible"(1)

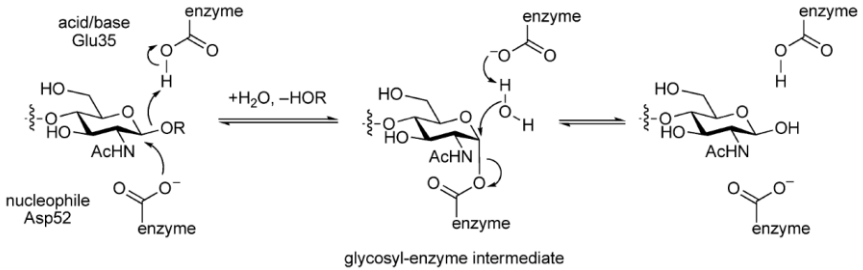
Drug Discovery Challenge

- **Reactivity:** less nucleophilic than cysteine, requiring more reactive warheads for effective engagement
- **Specificity:** more abundant than cysteine on protein surfaces(2), making selectivity challenging



Nature's Enzymatic Solution

- Protein surface can shift pK_a, precisely position substrates, and exclude water to substantially increase side chain reactivity
- Protein-substrate interactions ensure specificity of reaction



(1) Lietman, C. D., et al. *American Society of Clinical Oncology Educational Book,* 2022, 42, 1-13.
(2) Adapted From: White, *Chemical Science* 2012, 3, 3488-3494

Stick (2009) Carbohydrates: The Essential Molecules of Life, *2nd Ed.*, 7, 253-284.

Like Natural Enzymes, the Tri-Complex can Overcome These Challenges

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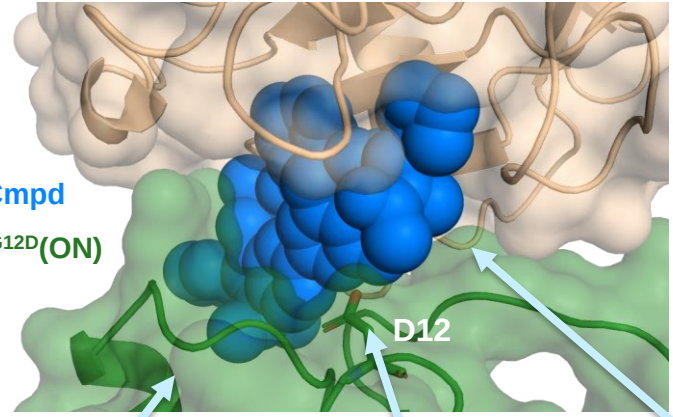
Engineer Binding Site to Increase Reactivity and Drive Specificity



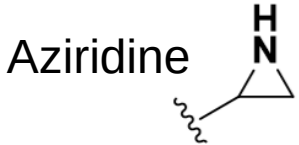
Noncovalent protein-protein and protein-ligand interactions

Change local electrostatic environment and exclude bulk water

Specificity to RAS(ON)

Precisely position and colocalize warhead and Asp 12

Screen of Carboxylate Reactive Functional Groups Identified Aziridines



Optimal Properties

- **Intrinsic Reactivity** ↓
- **On-Target Reactivity** ↑
- **Drug-like Properties** ↑

Compound 2 Represents Our First RAS(ON) G12D-Selective Covalent Inhibitor

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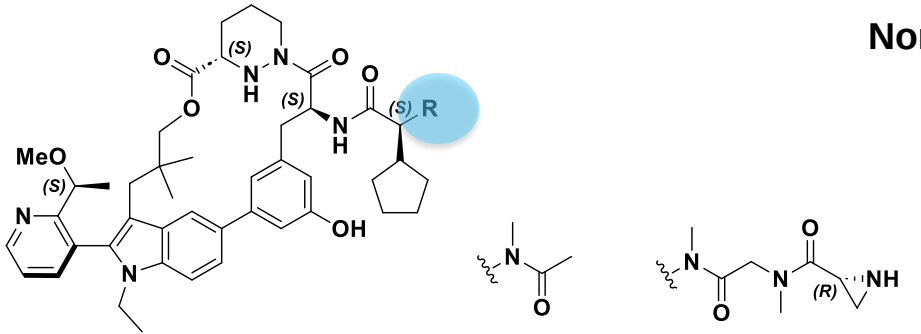
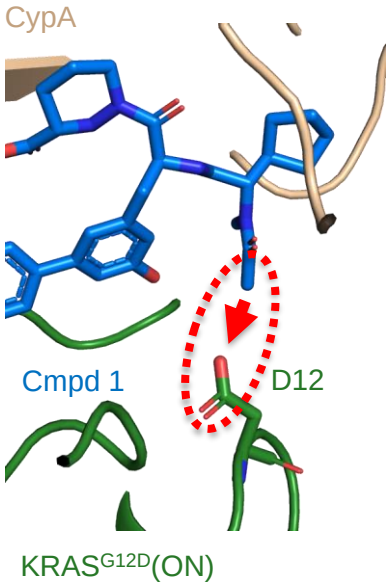
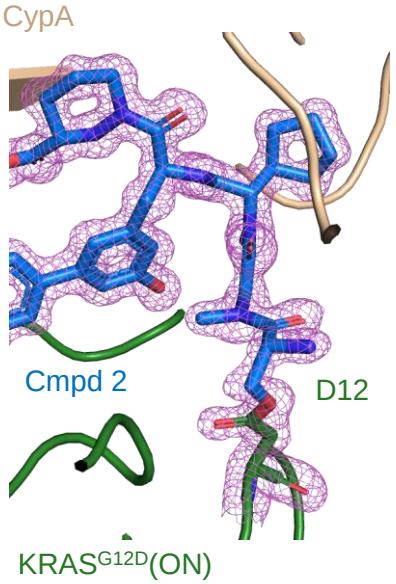


	Cmpd 1	Cmpd 2
$KRAS^{G12D}$(ON) Crosslinking 6h (%)	0	34
AsPC-1 pERK EC_{50} (nM)	158	55
AsPC-1 CTG EC_{50} (nM)	334	54

Noncovalent Cmpd 1 Affords a Vector for Warhead



Cmpd 2 has Continuous Density to D12



X-Ray $KRAS^{G12D}$(ON) with Cmpd 1 or 2

Incorporation of the Spiro[4.4] Linker Enhanced Crosslinking with the D12 Residue

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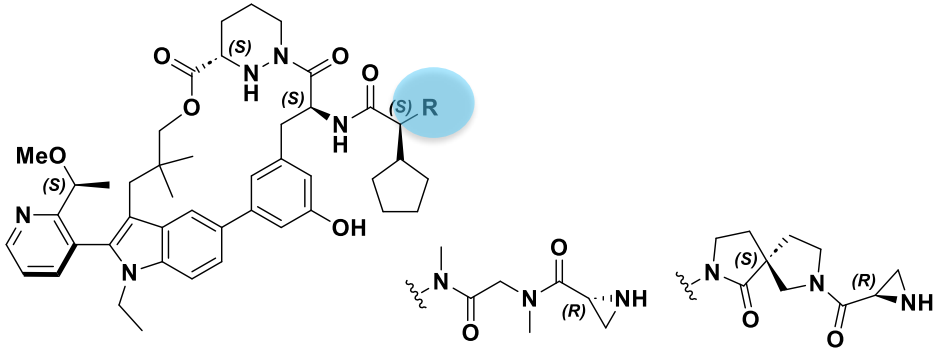
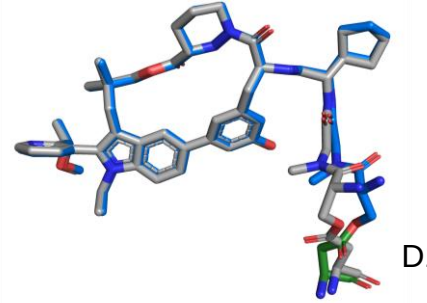
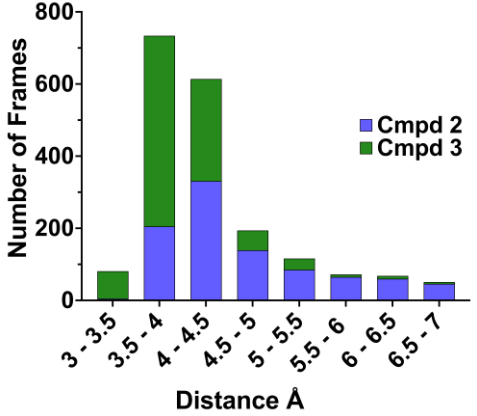


	Cmpd 2	Cmpd 3
KRAS^{G12D}(ON) Crosslinking 6h (%)	34	71
AsPC-1 pERK EC_{50} (nM)	55	81
AsPC-1 CTG EC_{50} (nM)	54	43

X-Ray KRAS^{G12D}(ON) with Cmpd 2 Shows Multiple Conformations Post Crosslinking



MD Shows Rigidification of the Linker in Cmpd 3 Keeps Aziridine Warhead in Closer Proximity to D12 Residue



Addition of Cyclopropyl to Aziridine Further Improved Crosslinking with the D12 Residue

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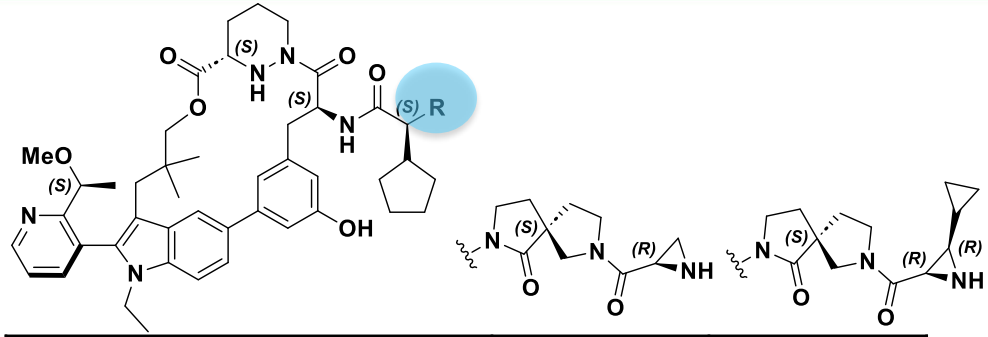
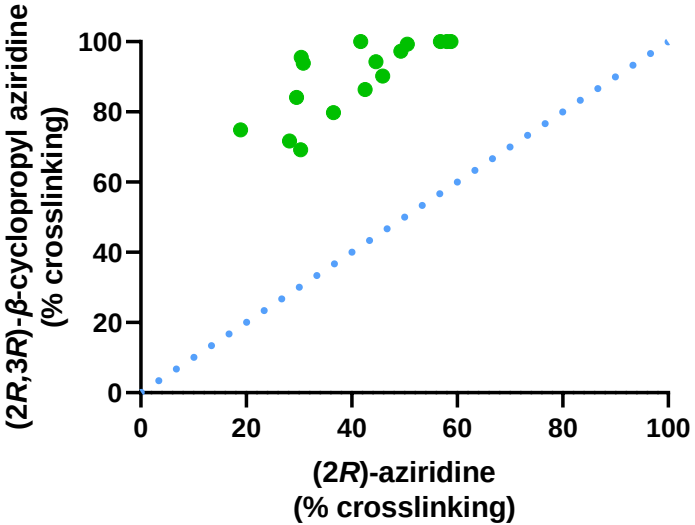


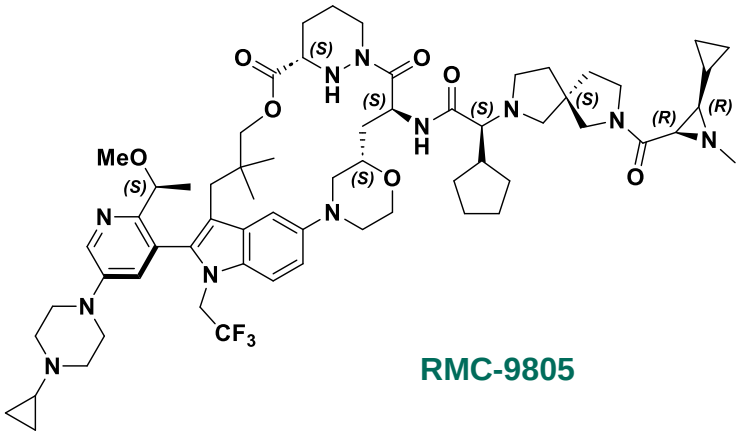
	Cmpd 3	Cmpd 4
KRAS^{G12D}(ON) Crosslinking 6h (%)	71	89
AsPC-1 pERK EC_{50} (nM)	81	27
AsPC-1 CTG EC_{50} (nM)	43	25
Simulated Gastric Fluid Stability ($T_{1/2}$, min)	>120	18
Kinetic Solubility (µM)	5	<2

Matched Pair Analysis Highlights How Cyclopropyl Substitution Increases Biochemical Crosslinking of KRAS^{G12D}(ON)



RMC-9805 Displays a High-Quality Drug-Like Profile

	RMC-9805
KRAS^{G12D}(ON) Crosslinking 6h (%)	86
k_{inact}/K_I ($M^{-1}s^{-1}$)	102
AsPC-1 pERK EC_{50} (nM)	23
AsPC-1 CTG EC_{50} (nM)	17
Kinetic Solubility (µM)	235
Simulated Gastric Fluid Stability ($T_{1/2}$, min)	>120
GSH Stability ($T_{1/2}$, min)	>120
Whole Blood Stability ($T_{1/2}$, min, x-species)	>120
% Oral Bioavailability Avg (x-species)	32
Clearance (x-species)	Moderate
Safety Panels and Cysteinome Screen	Low Risk



RMC-9805

RMC-9805 is Highly Selective for Crosslinking RAS^{G12D}(ON)

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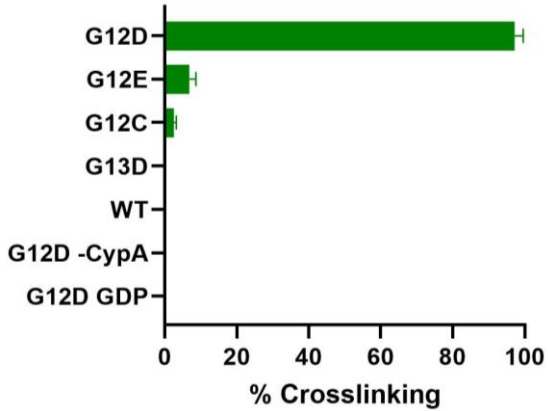
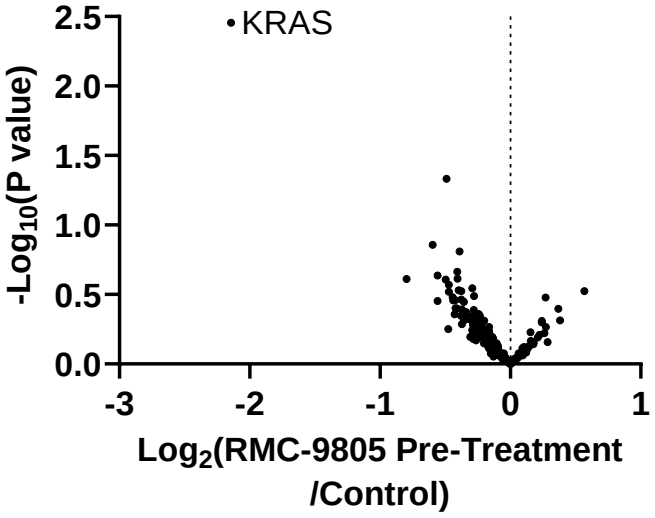
Selective Modification of the G12D Mutant Allele in RAS Proteins in Cells

CypA-Dependent and Selective Biochemical Modification of KRAS^{G12D}(ON)



Selective Inhibition of Click IP Probe Binding in KRAS$^{G12D/G12D}$ Cells



RMC-9805 RMC-9805 Click IP probe

RMC-9805 Modulates RAS Pathway Signaling and Induces Apoptosis in KRAS^{G12D} Xenograft Tumors *in Vivo*

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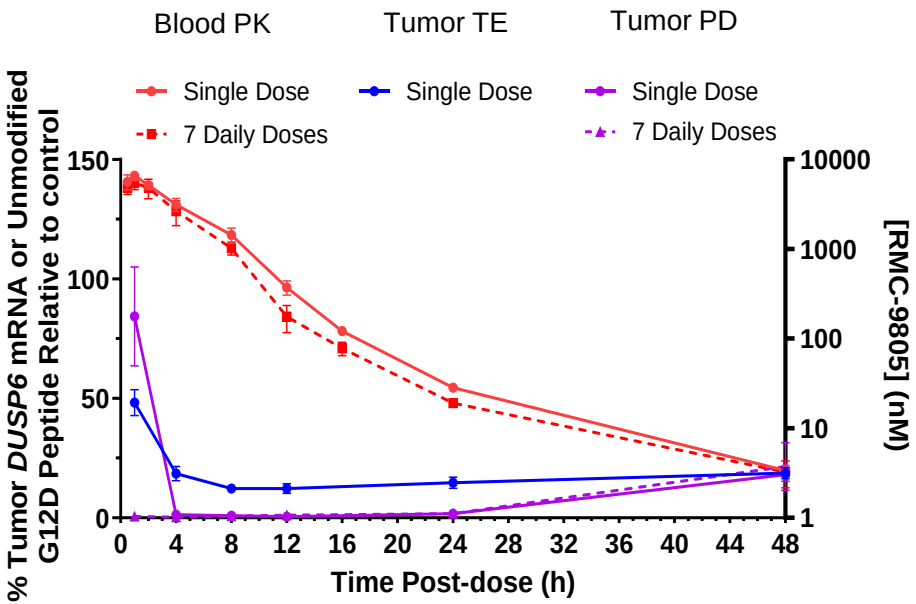
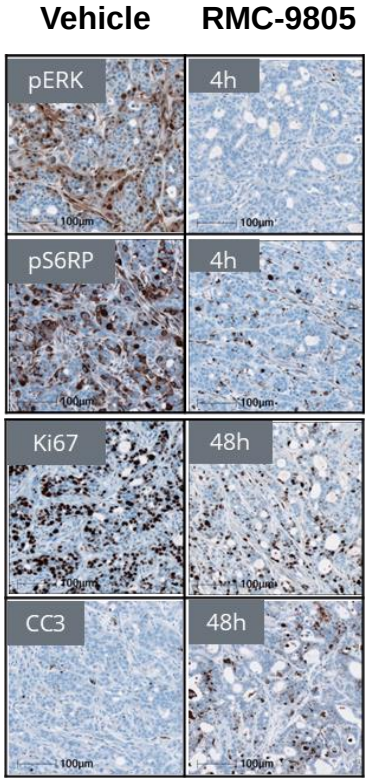
HPAC CDX (PDAC, KRAS$^{G12D/WT}$)

RMC-9805 100 mg/kg po qd





RAS pathway signaling

Proliferation

Apoptosis

Post a Single Oral Dose

Histopathology data collected at indicated time points after a single dose. Images of 20X magnification shown.

RMC-9805 Drives Regressions of KRAS^{G12D} Xenograft Models at Well-Tolerated Doses *in Vivo*

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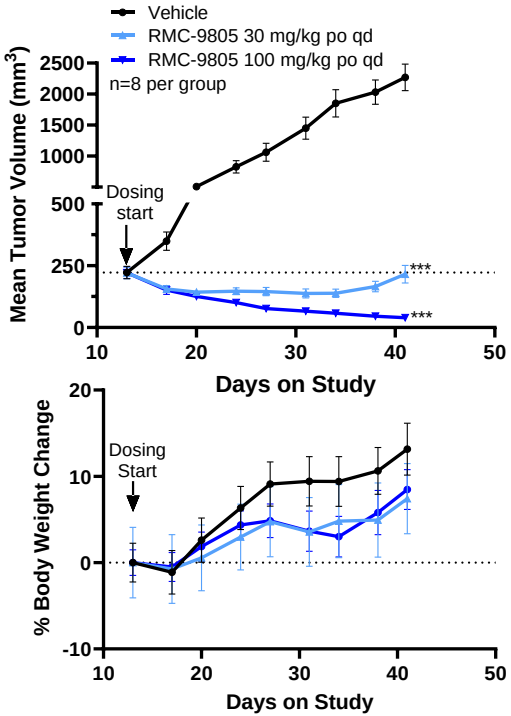
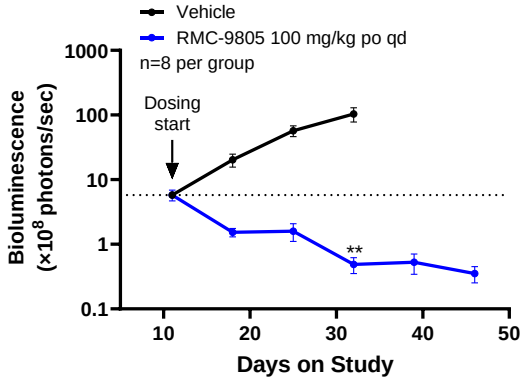
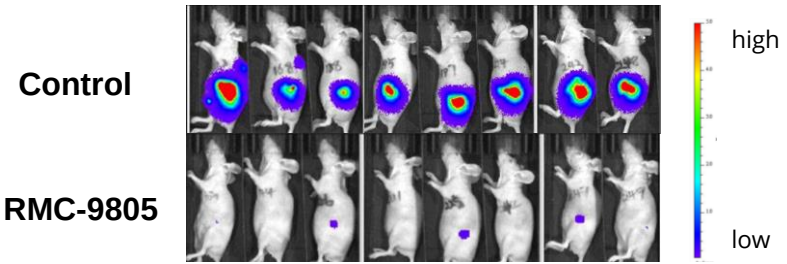
HPAC CDX (PDAC, KRAS$^{G12D/WT}$)

Subcutaneous Xenograft



HPAC-Luciferase Pancreas Xenograft





** p<0.01, ***p<0.001 as compared to control at end of study, two-way repeated measures ANOVA

RMC-9805 Drives Deep and Durable Regressions Across Diverse KRAS^{G12D} Cancer Models *in Vivo*

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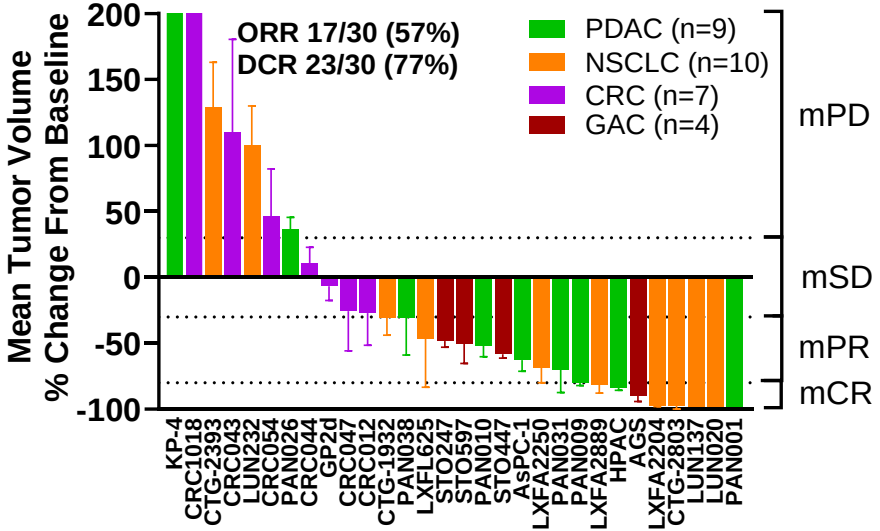
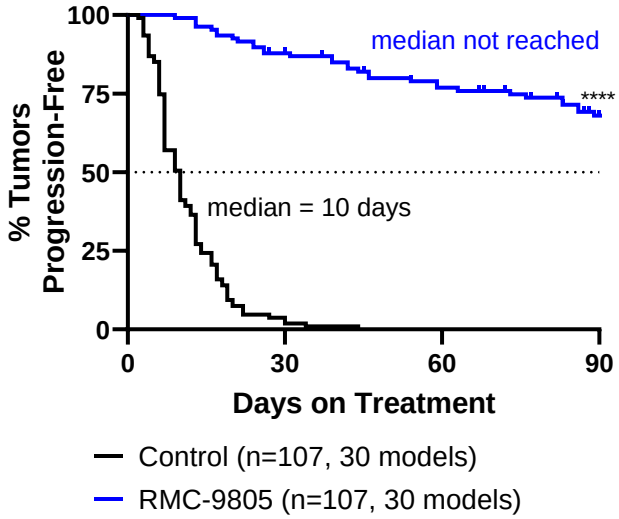
Responses



Durability



****p<0.0001 by Log-rank test (RMC-9805 vs Vehicle control treatment)

Revolution Medicines preclinical research as of 08/30/23
RMC-9805 dosed at 100 mg/kg po qd; n=2-8/group
Responses after 28 ± 2 days of treatment unless maximal tumor burden reached sooner or control tumor reached 2 doublings (4* initial TV) later
Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015)
Progression defined as tumor doubling from baseline

Chemical Leverage of Aspartic Acid by Covalent RAS(ON) G12D-selective Inhibitors *is Possible*

- RMC-9805 is an orally bioavailable, RAS(ON) G12D-selective covalent inhibitor
- RMC-9805 induces deep and durable regressions in $KRAS^{G12D}$ tumors across histotypes
- RMC-9805-001, a phase 1/1b first-in-human study, is ongoing*
- Interim observations previously disclosed (January 2024):
  - RMC-9805 demonstrated oral bioavailability in patients and exhibited pharmacokinetics consistent with expectations from preclinical data
  - RMC-9805 cleared multiple dose levels and favorable tolerability was observed with no dose-limiting toxicities reported thus far

*https://www.clinicaltrials.gov/study/NCT06040541

Acknowledgements

- The patients and investigators who are making clinical evaluation of RMC-9805 possible
- Revolution Medicines Research and Development Teams