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MOLECULAR TARGETS AND CANCER THERAPEUTICS
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Targeting RAS-Addicted Cancers with Investigational RAS(ON) Inhibitors

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AACR American Association for Cancer Research
NIH NATIONAL CANCER INSTITUTE
EORTC European Organisation for Research and Treatment of Cancer

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I have the following relevant financial relationships to disclose:

- Employee of: Revolution Medicines
- Stockholder in: Revolution Medicines

I will not discuss off-label use in my presentation.

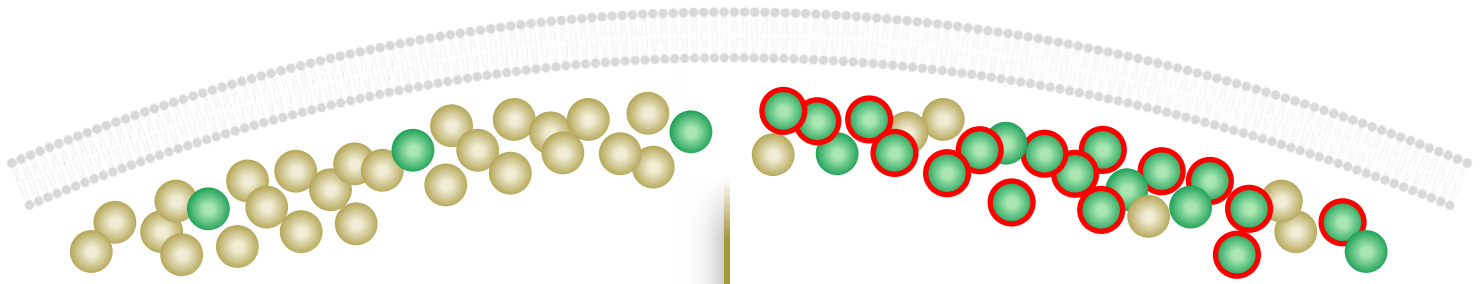
I will discuss the potential for investigational use of RAS(ON) inhibitors in my presentation.

Excessive RAS(ON) Signaling Drives 30% of Human Cancers

RAS(OFF)

RAS(ON)

Normal



Tightly regulated
RAS(ON) proteins control cell growth

RAS-Addicted Cancers

RAS Cancer Mutations

Excessive
RAS(ON) signaling drives uncontrolled cell growth

Example mutations in KRAS, HRAS and/or NRAS	G12C, G12D, G12V, G12R G13C, G13D Q61H, Q61K, Q61L

New patients per year (US)[1]

>200,000
Including

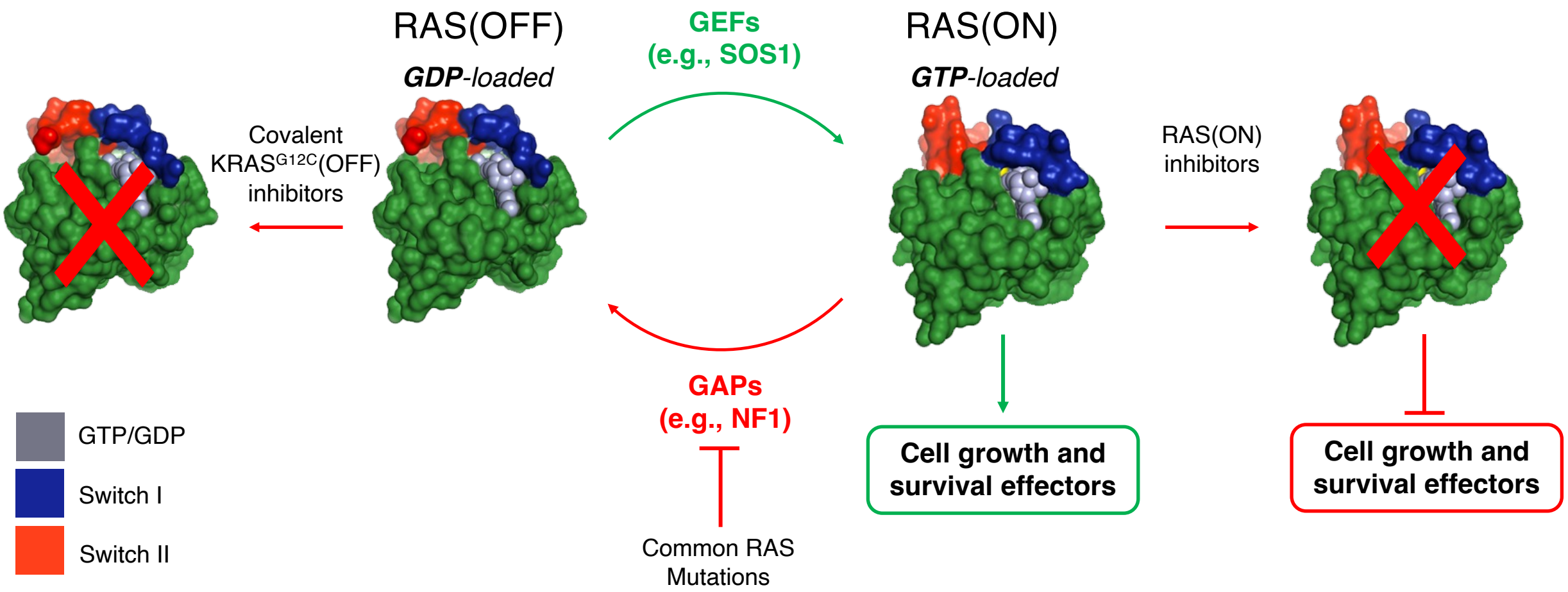
60,000
Lung cancer
(29% of NSCLC)

75,000
Colorectal cancer
(49% of CRC)

53,000
Pancreatic cancer
(92% of PDAC)

1. Estimated using tumor mutation frequencies from Foundation Medicine Insights August 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023.
CRC, colorectal cancer, PDAC pancreatic cancer, NSCLC, non-small cell lung cancer; RAS, rat sarcoma.

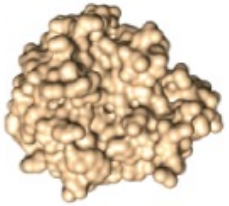
Targeting RAS(ON) Directly Disrupts Oncogenic Signaling but Has Historically Proved Challenging



GAP, GTPase-accelerating proteins; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factors; GTP, guanosine triphosphate; NF1, neurofibromatosis 1; SOS, son of sevenless homolog 1.

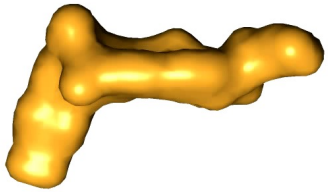
RAS(ON) Inhibitors Remodel the Surface of Cyclophilin A to Bind Tightly to RAS(ON)

RAS(ON)

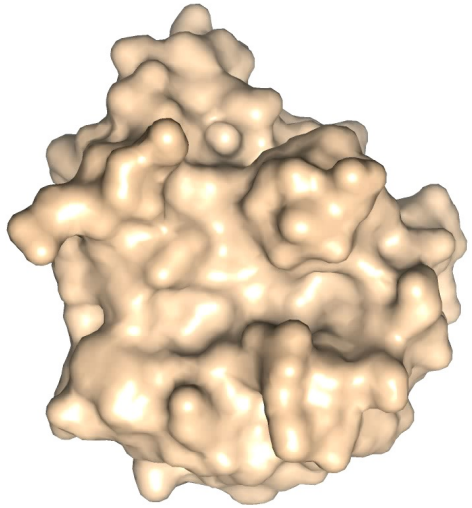


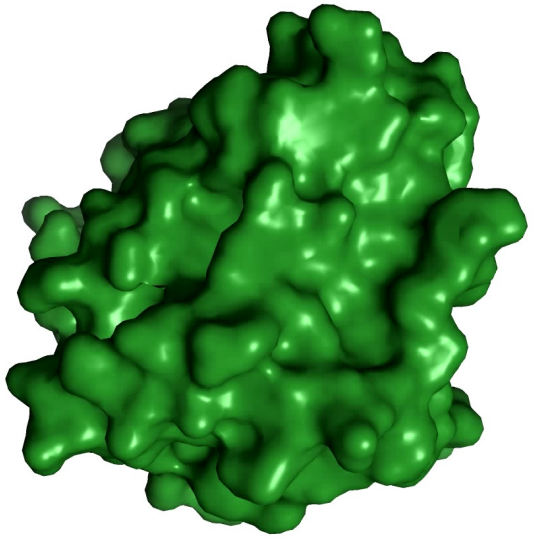
Cyclophilin A

RMC Tri-complex inhibitor



RAF RBD





Co-crystal structure of RMC-7977 with cyclophilin A, RevMed preclinical data;
Pre-print: Singh et al, **Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy, DOI: https://doi.org/10.21203/rs.3.rs-3122478/v1**

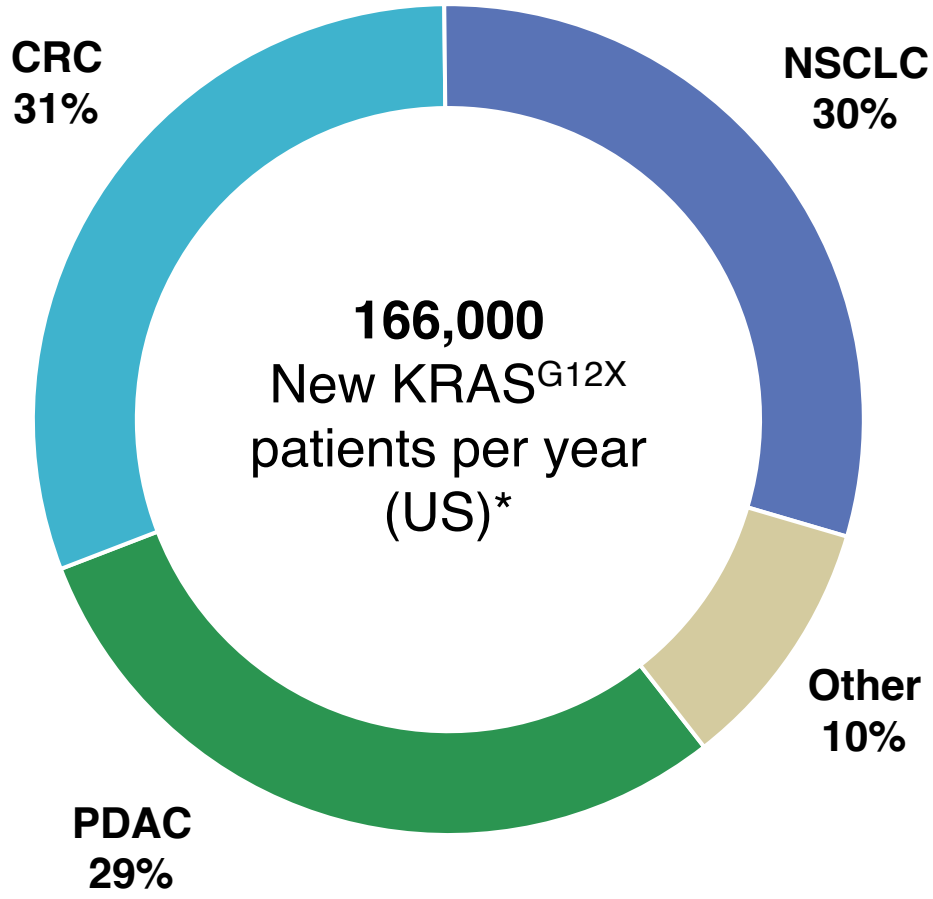
Development-Stage RAS(ON) Inhibitor Portfolio Designed to Treat Nearly All Patients with RAS-Mutated Cancers

		RAS Selectivity
MULTI		
RMC-6236	Clinical	Multiple mutants (initial focus on G12) and wild-type
Mutant-Selective		
RMC-6291	Clinical	G12C
RMC-9805	Clinical	G12D
RMC-5127	IND-enabling	G12V
RMC-0708	IND-enabling	Q61H
RMC-8839	IND-enabling	G13C

>200,000 New RAS cancer patients/year (US)

IND, investigational new drug.

RMC-6236: First-in-Class, RAS^{MULTI}(ON) Inhibitor with Broad Potential Against RAS-Addicted Cancers



Highly Potent and Selective RAS(ON) Inhibitor

- Suppresses diverse mutant RAS cancer drivers and cooperating wild-type RAS proteins

Robust Anti-Tumor Activity in Cancer Models

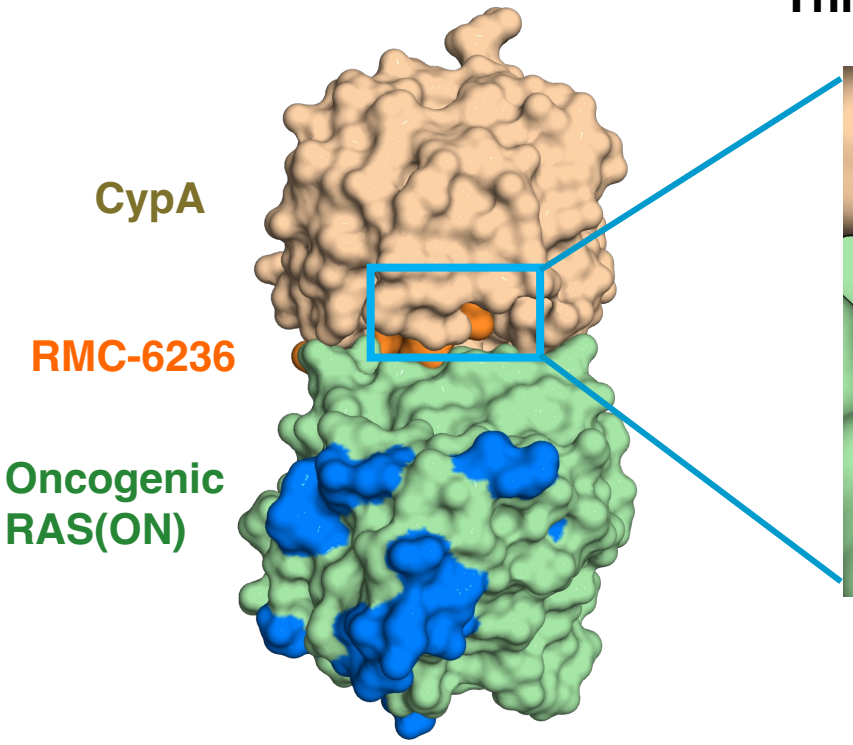
- Deep and sustained inhibition drives durable anti-tumor activity in tumors with common RAS variants

Attractive PK/ADME Profile

- Favorable *in vivo* oral bioavailability, clearance, and concentration in tumors for effective target coverage in RAS-addicted cancer cells

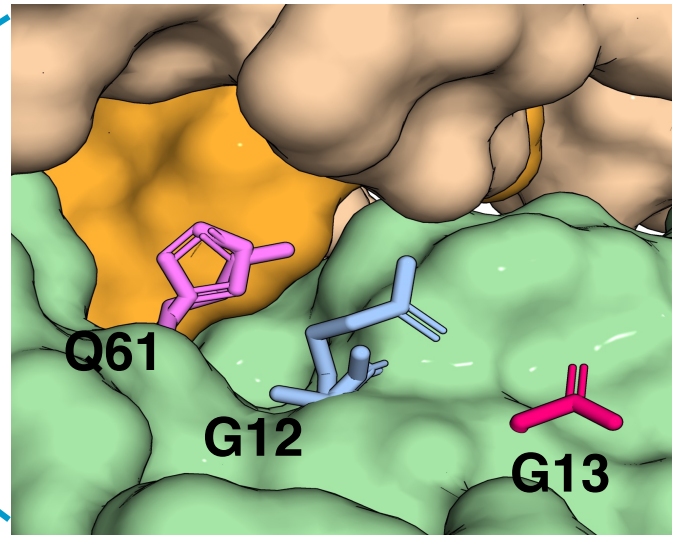
*New patients per year rounded to nearest 1000. PDAC, pancreatic ductal adenocarcinoma. NSLC non-small cell lung cancer; CRC colorectal cancer

RMC-6236 is a Non-Covalent Inhibitor of Multiple Mutant and Wild-Type RAS(ON) Variants

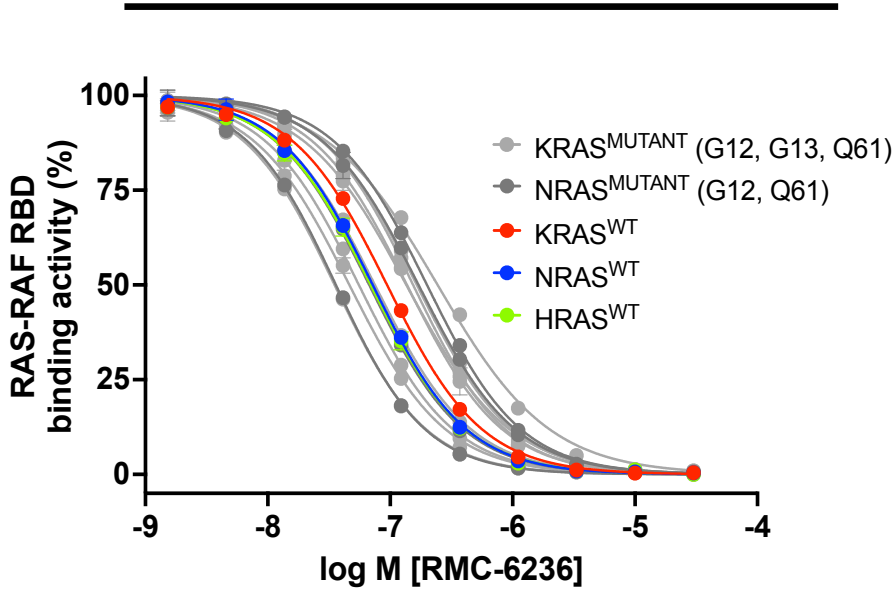


K, H, NRAS divergent residues

Three Mutational Hotspots in RAS

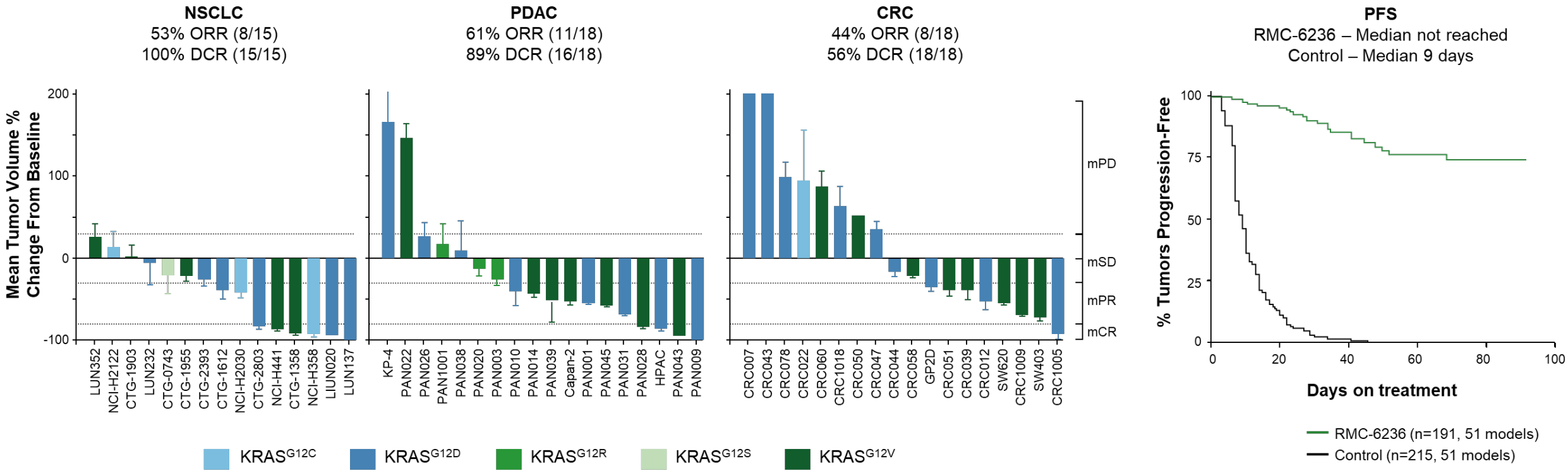


Biochemical (TR-FRET)



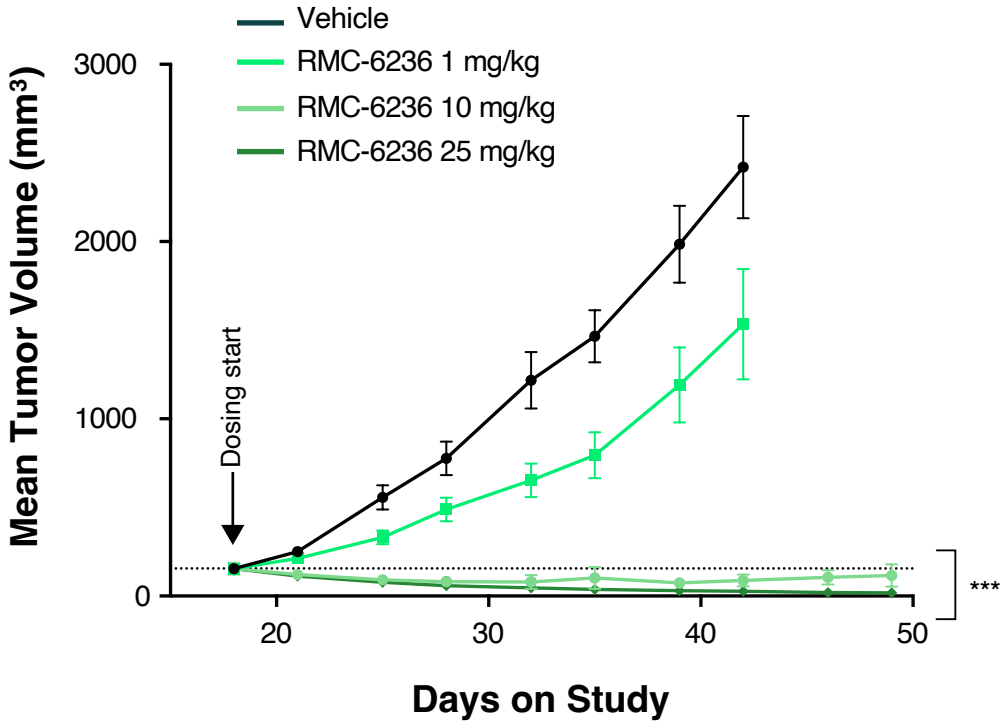
CRD, cysteine-rich binding domain; TR-FRET, time-resolved fluorescence with Förster's resonance energy transfer.

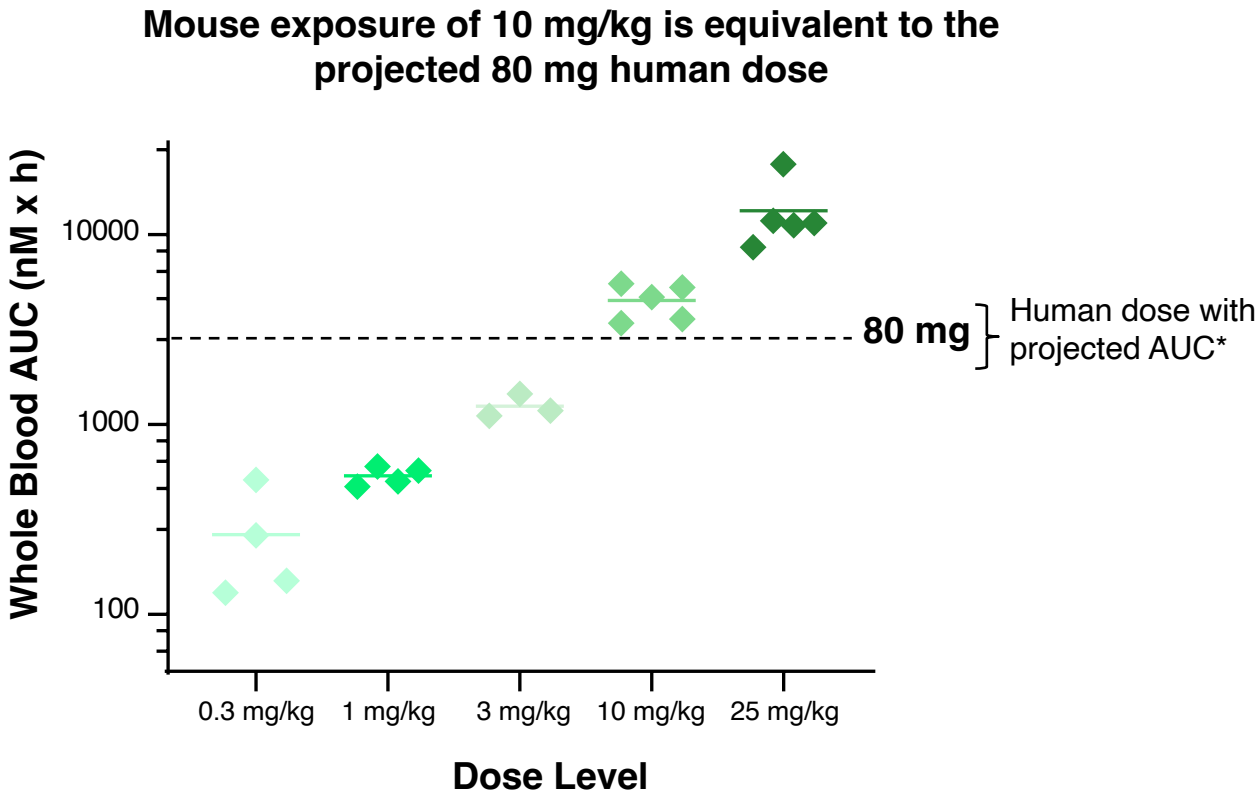
RMC-6236: Highly Active with Durable Effect Across in Vivo Models of Major Human Cancers with RAS Mutational Drivers



Revolution Medicines preclinical research as of June 1, 2022.
RMC-6236 dosed at 25 mg/kg PO QD; n=1–10/group; progression defined as tumor doubling from baseline.
Responses assigned according to mRECIST.
DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival; PO, orally; QD, once daily.

Preclinical Models Project Human Exposures at Which to Expect Tumor Regressions





NCI-H441 CDX; NSCLC, KRAS$^{G12V/WT}$; all doses given PO, QD.
*Projected human exposure converted to mouse equivalent exposure based on blood/plasma partitioning and plasma protein binding.
AUC, area under the curve; CDX, cell line-derived xenograft.

RMC-6236-001 Ongoing Phase 1 Study Design (NCT05379985)

Key Eligibility Criteria

- Advanced solid tumors with $KRAS^{G12X}$ mutations (currently excluding $KRAS^{G12C}$)
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

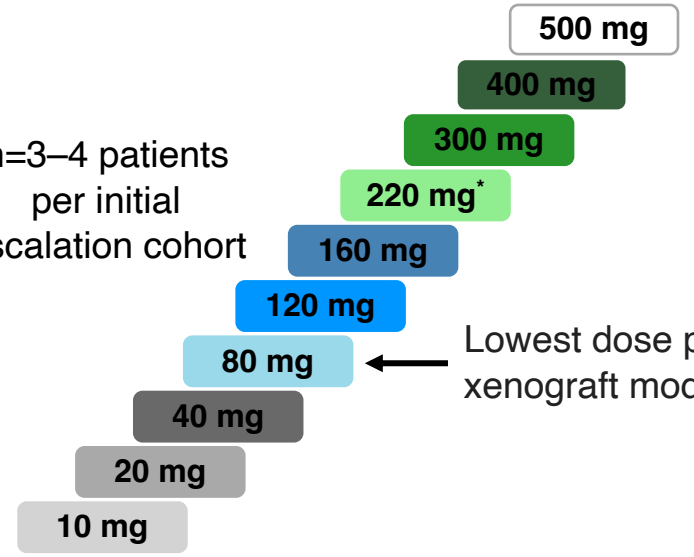
Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD, 21-day treatment cycle

n=3–4 patients per initial escalation cohort



Lowest dose projected to induce tumor regressions in human xenograft models with $KRAS^{G12X}$ mutations in mice[1]

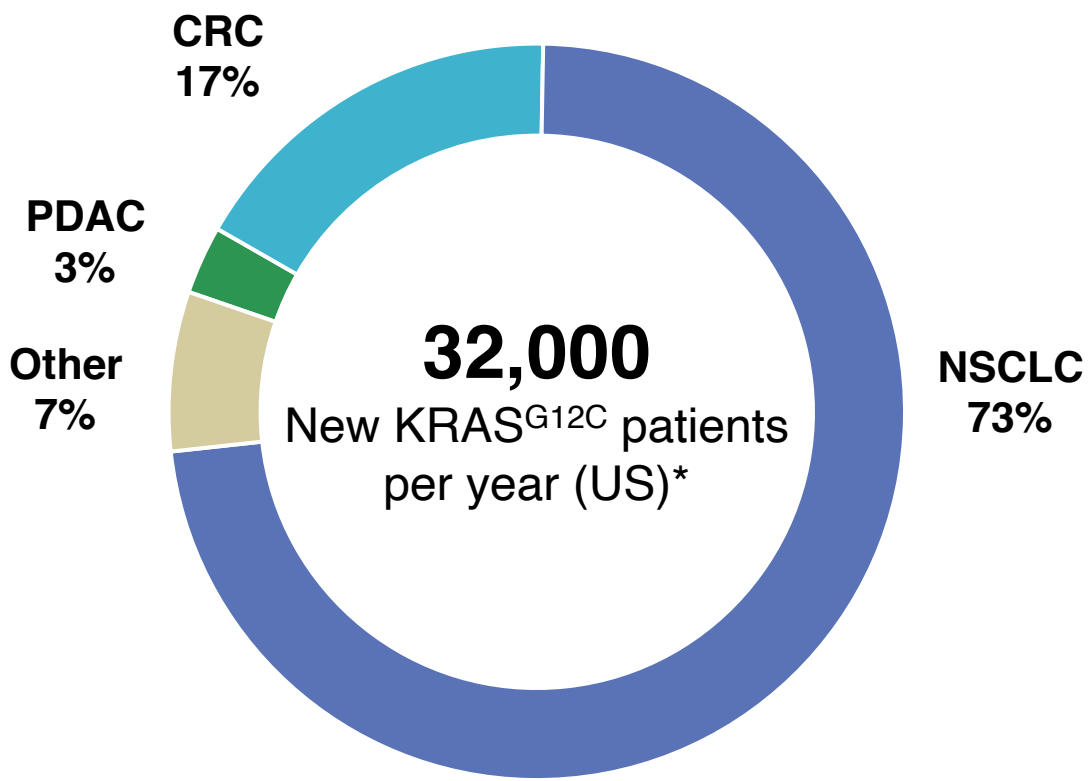
Dose Expansion / Optimization

Initial data on safety and pharmacokinetics, AACR-NCI-EORTC, Poster #B032, Spira et al, Oral Presentation today Oct 13, Plenary Session 4: New Drugs on the Horizon

Initial data on anti-tumor activity in NSCLC and PDAC Oral to be presented Sunday Oct 22 ESMO Congress, Madrid, Spain, Arbour et al, Proffered Paper session – Developmental therapeutics

$KRAS^{G12X}$ defined as mutation at codon 12, which encodes glycine (G), to X where X = A, D, R, S, or V.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

RMC-6291: Clinical Stage, Mutant-Selective, Covalent RAS(ON) Inhibitor with Best-in-Class Potential for KRAS^{G12C} Cancers



*New patients per year rounded to nearest 1000.

Preclinical Profile

Highly Potent and Selective RAS(ON) Inhibitor

- Highly active against KRAS^{G12C}
- Covalent for irreversible inhibition
- Low off-target risk and acceptable safety profile

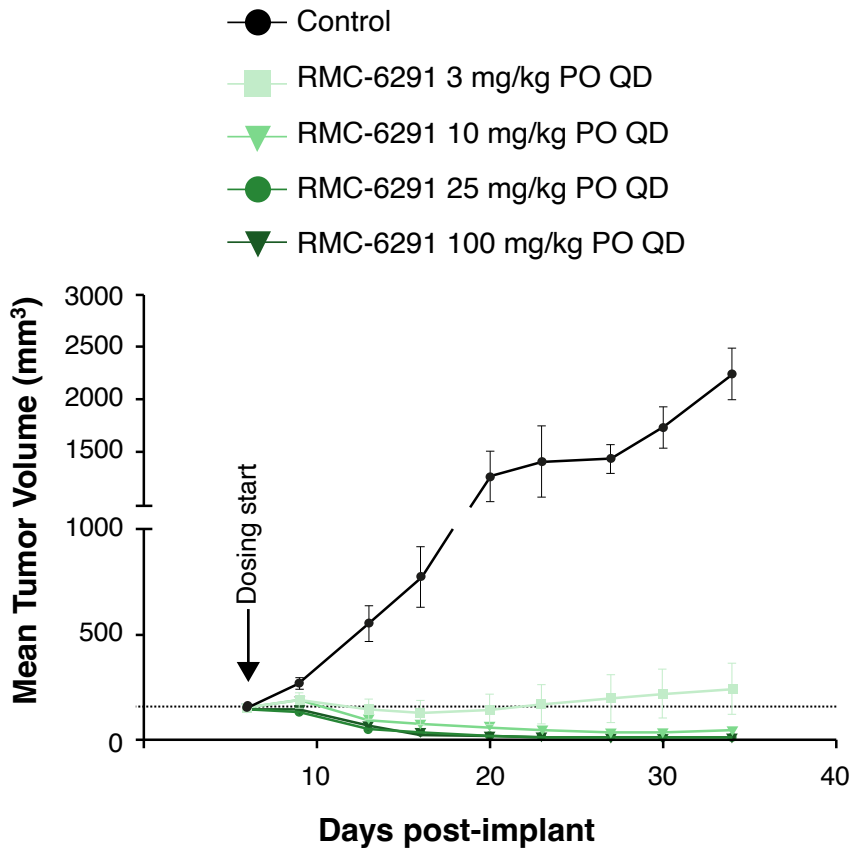
Robust Anti-Tumor Activity in Cancer Models

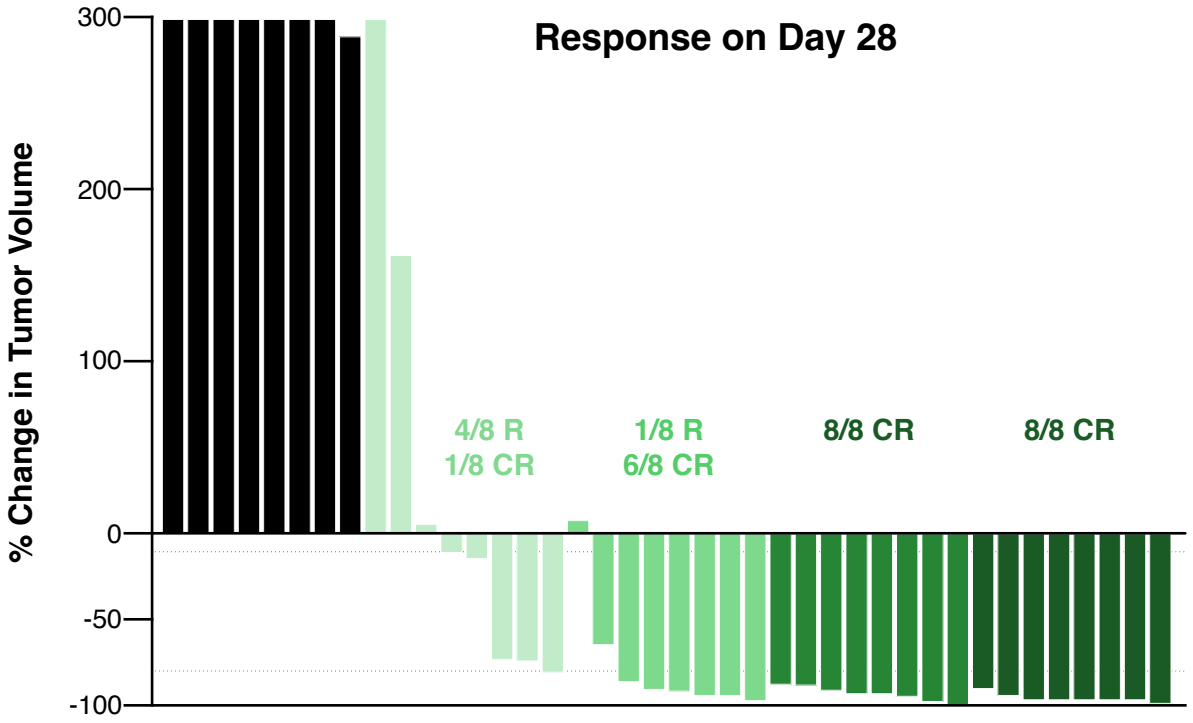
- Rapid, deep and sustained inhibition drives durable anti-tumor effects across multiple KRAS^{G12C} tumor types, with complete responses in some models

Attractive PK/ADME Profile

- Favorable *in vivo* oral bioavailability and clearance for effective target coverage in KRAS^{G12C}-addicted cancer cells

RMC-6291 Drives Tumor Regressions at Low Doses in Preclinical Models of KRAS^{G12C}–Mutant NSCLC

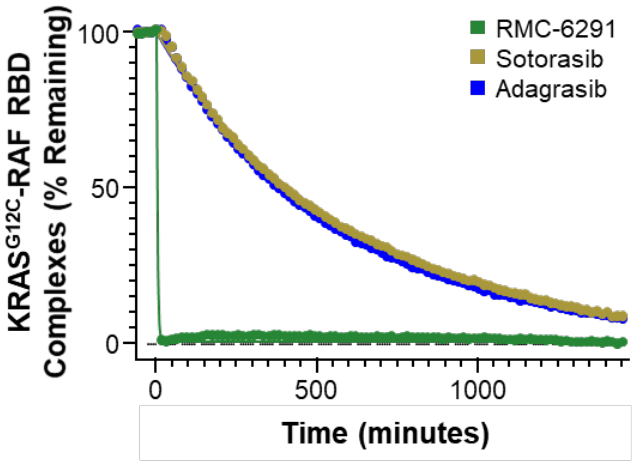




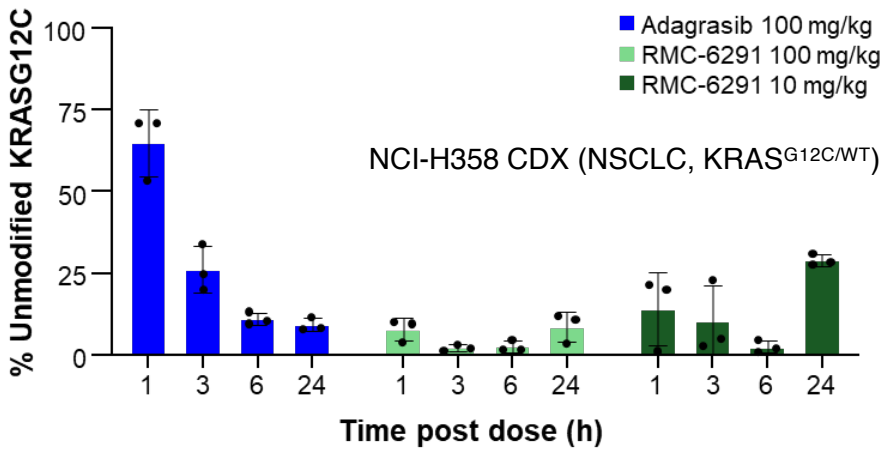
Revolution Medicines preclinical research. NCI-H358 CDX (NSCLC, KRAS$^{G12C/WT}$); all doses given orally, once daily.
R, number of regressions >10% from initial; CR, number of regressions ≥80% from initial; each animal is represented as a separate bar in the waterfall plot.

Advantage of a RAS(ON) Inhibitor: Rapid Target Engagement and Insensitivity to Adaptive Resistance

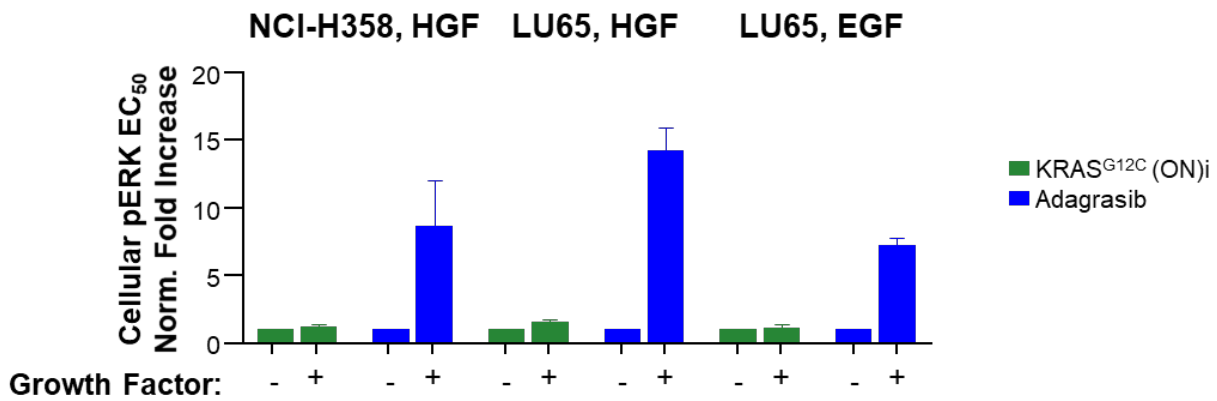
Rapid RAS(ON)-CRAF Complex Disruption (*in Vitro*, Cell)

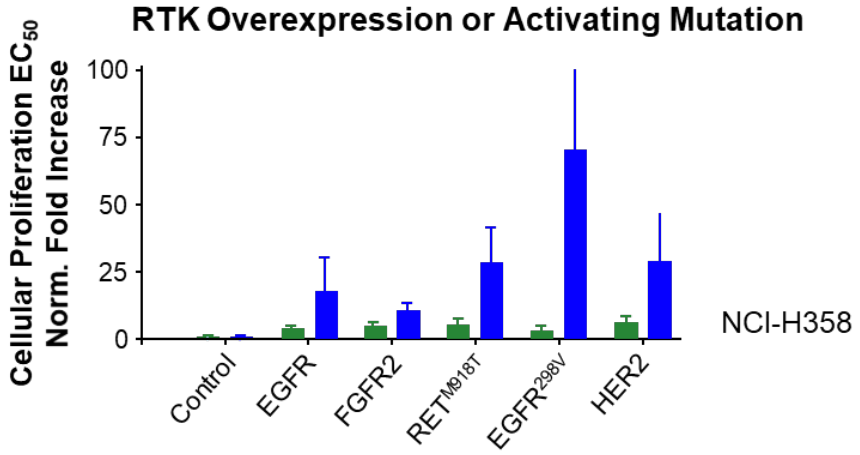


Rapid KRAS^{G12C} Covalent Modification (*in Vivo,* Tumor)



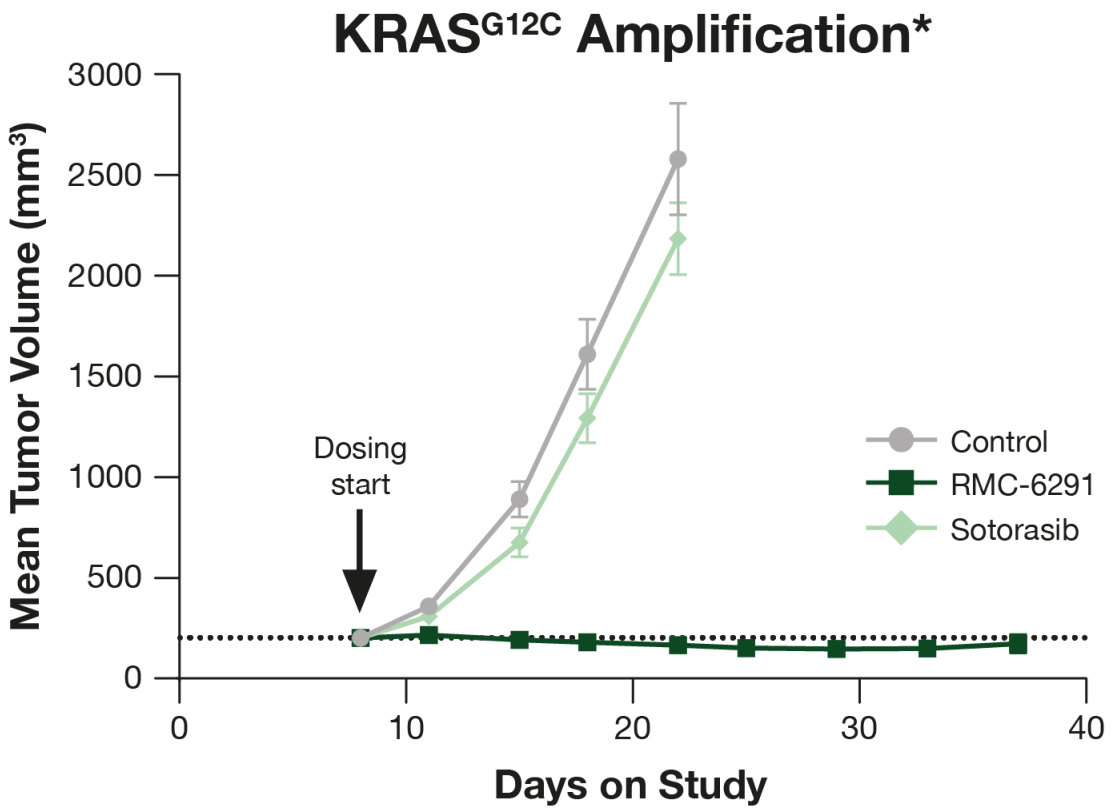
Insensitivity to Non-Genomic and Genomic Mechanisms of Resistance

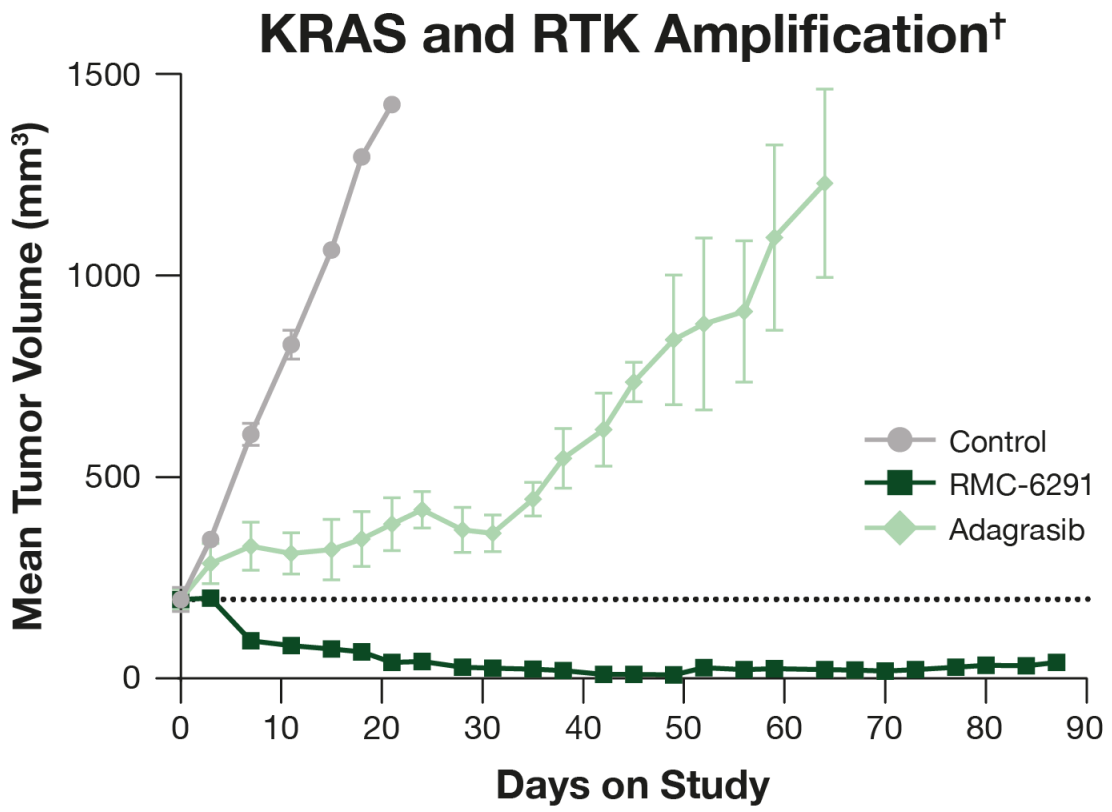




EGF, epidermal growth factor; HGF, hepatocyte growth factor; pERK, phosphorylated extracellular signal-regulated kinas; RTK, receptor tyrosine kinase.

RMC-6291 Drives Tumor Regressions in Preclinical Models of KRAS^{G12C}(OFF) Inhibitor Clinical Resistance





Revolution Medicines preclinical research.
1. Sotorasib-Resistant MIA PaCa-2 CDX (PDAC, KRAS$^{G12C/G12C}$, KRAS^{amp}); RMC-6291 dosed at 100 mg/kg PO QD; sotorasib dosed at 100 mg/kg PO QD;
2. LUN055 PDX (NSCLC, KRAS$^{G12C/WT}$, ERBB3amp, KRAS^{amp}); RMC-6291 dosed at 200 mg/kg PO QD; adagrasib dosed at 100 mg/kg PO QD.

RMC-6291-001 Phase I Study Design (NCT05462717)

Key Eligibility Criteria

- Advanced solid tumors with KRAS^{G12C} mutations
- Received prior standard therapy including treatment with KRAS^{G12C}(OFF) inhibitors
- ECOG PS 0–1
- No active brain metastases

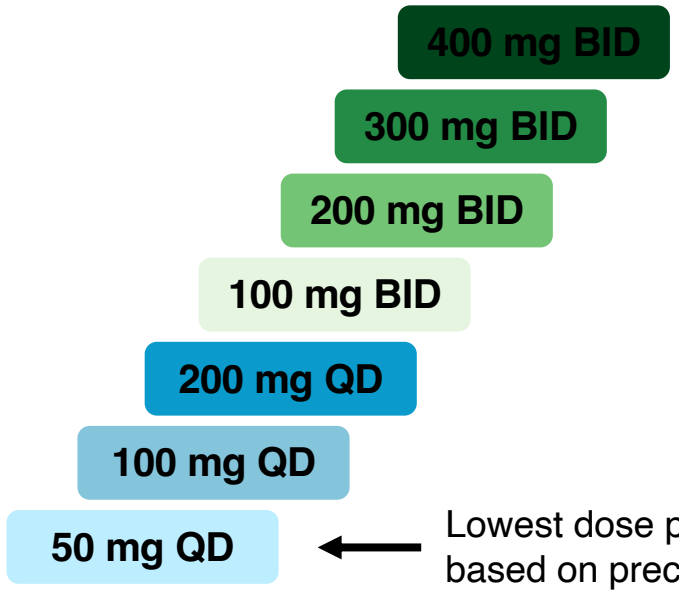
Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Initial data on safety and anti-tumor activity, AACR-NCI-EORTC, Jänne et al, Oral Presentation today Oct 13, Spotlight on Proffered Papers 2

Dose Escalation

RMC-6291 administered orally QD or BID, 21-day treatment cycle



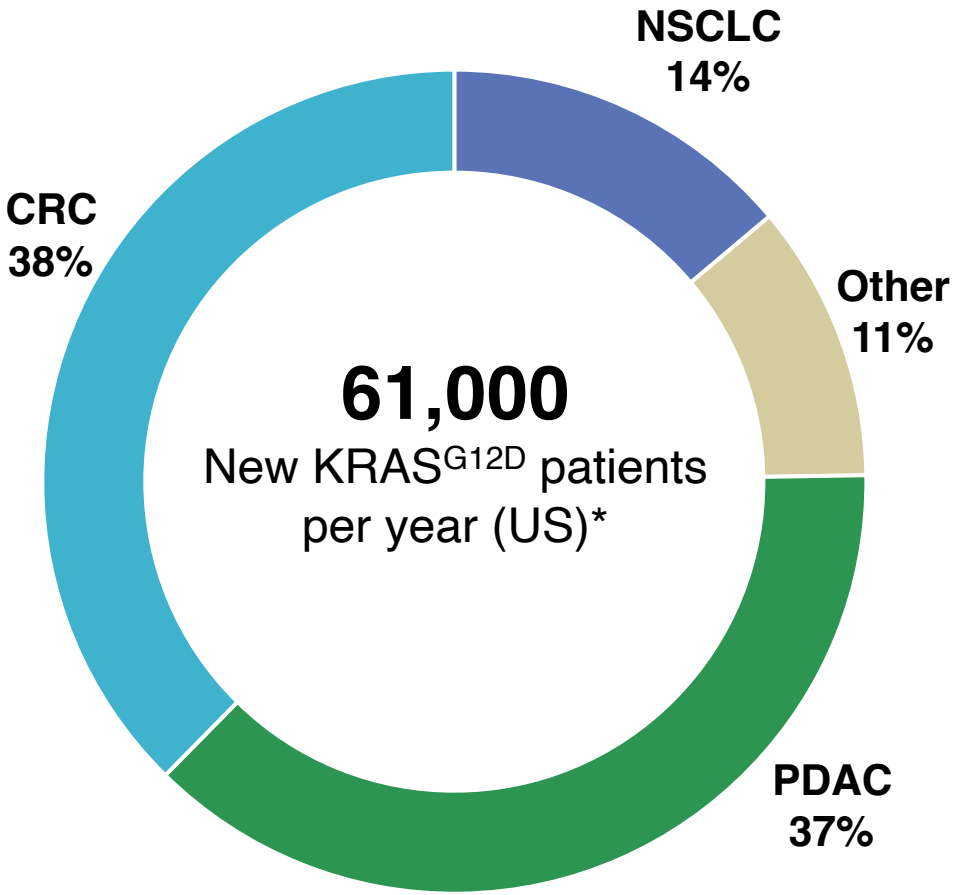
Lowest dose projected to drive tumor regression in humans based on preclinical models.

Additional patients with NSCLC and CRC were enrolled at dose levels that cleared DLT evaluation (backfill enrollment and dose optimization).

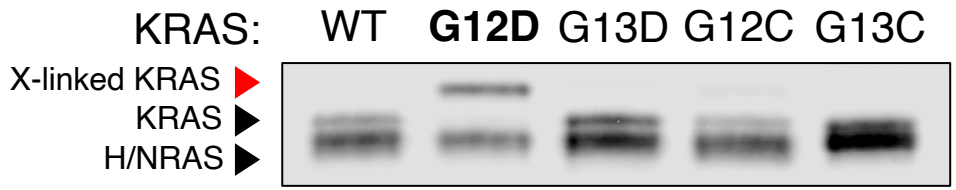
Dose Expansion / Optimization

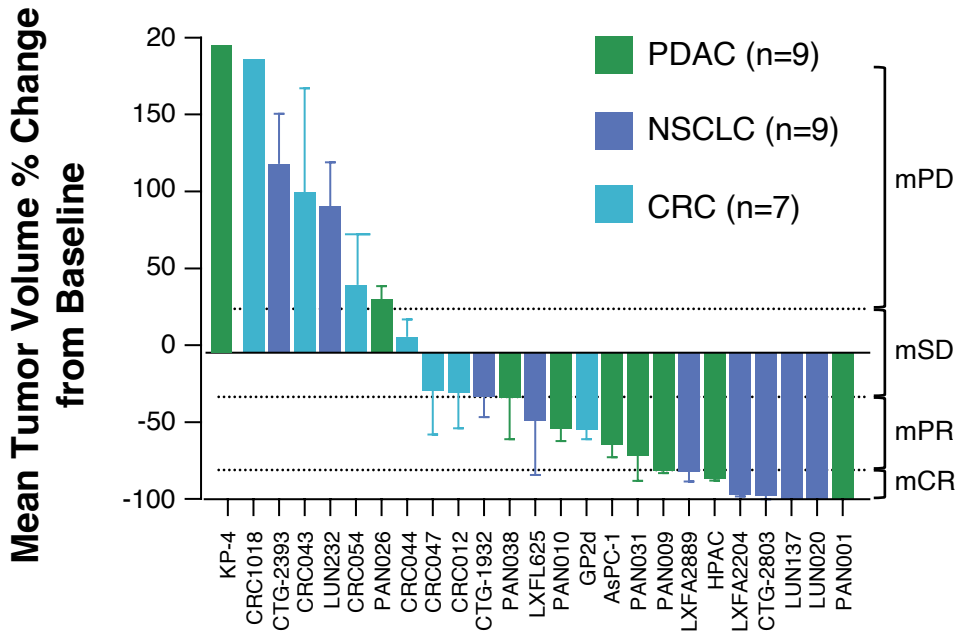
BID, twice daily.

RMC-9805: Clinical Stage, Mutant-Selective, Covalent RAS(ON) Inhibitor for KRAS^{G12D}–Mutant Cancers (NCT06040541)



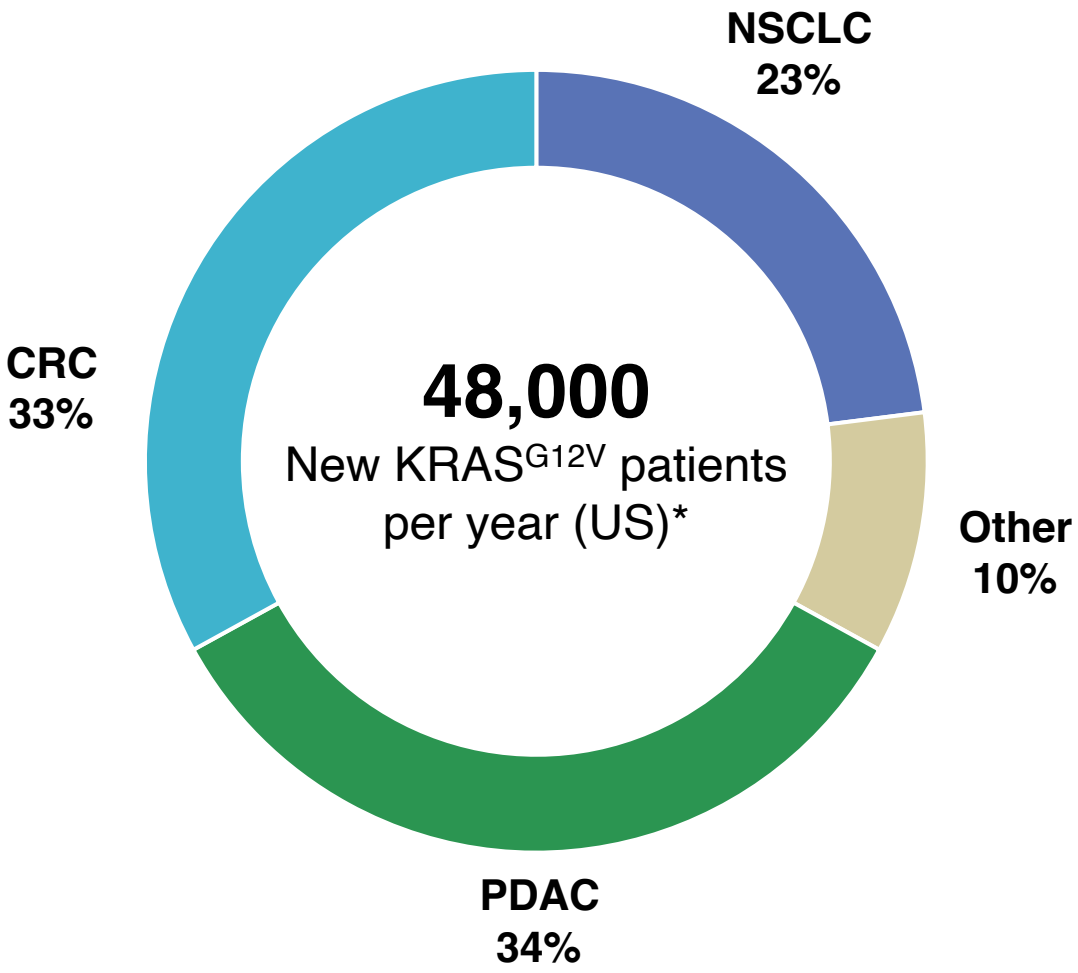
Selective Covalent Binding to KRAS^{G12D}(ON)



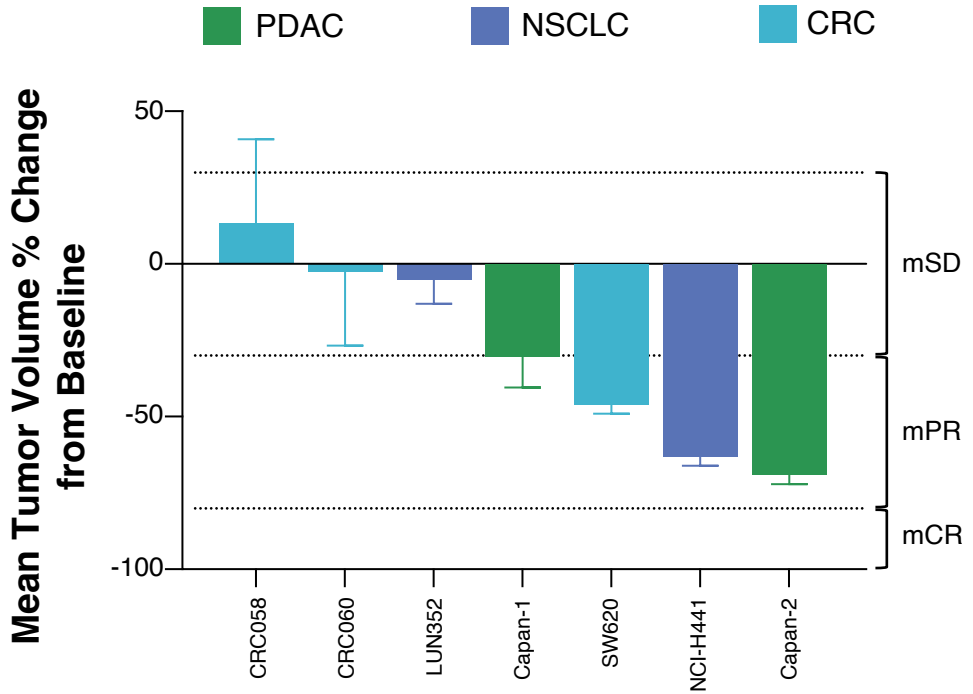


*New patients per year rounded to nearest 1000.

RMC-5127: First-in-Class Mutant-Selective RAS(ON) Inhibitor for KRAS^{G12V}-Mutant Cancers



In Vivo Anti-Tumor Activity Across KRAS^{G12V} Cancer Models



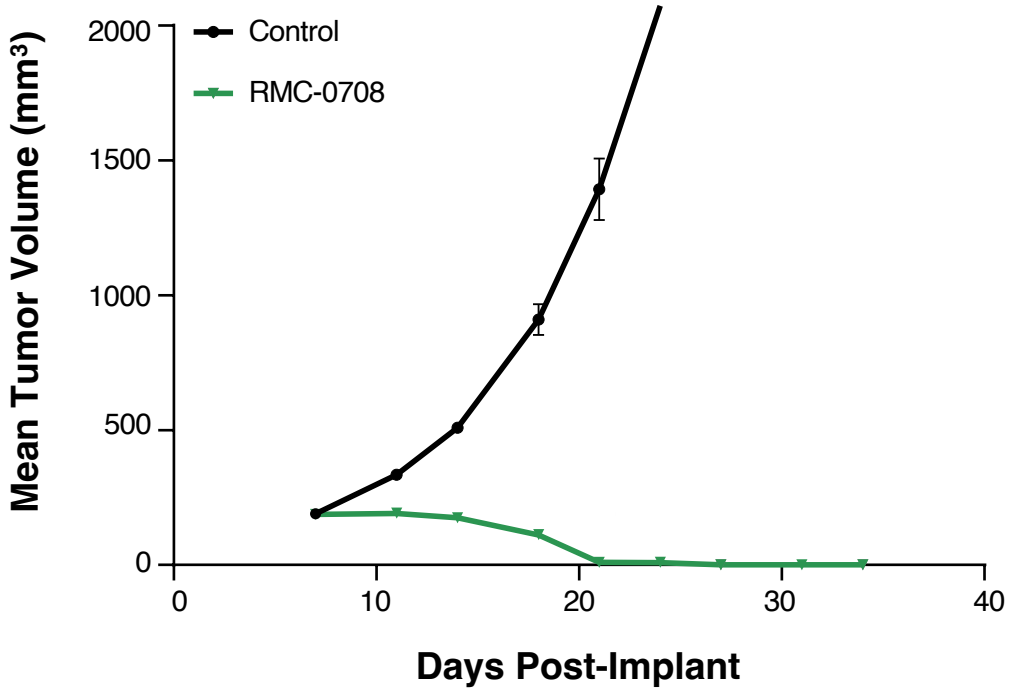
*New patients per year rounded to nearest 1000.
mCR, molecular complete response; mPR, molecular partial response; mSD, molecular stable disease.

Data for KRAS^{G12V} RAS(ON) inhibitor to be presented in Poster Session B, AACR-NCI-EORTC, Lee et al.

First-in-Class Mutant-Selective RAS(ON) Inhibitors Targeting $KRAS^{Q61H}$ and $KRAS^{G13C}$ Cancers

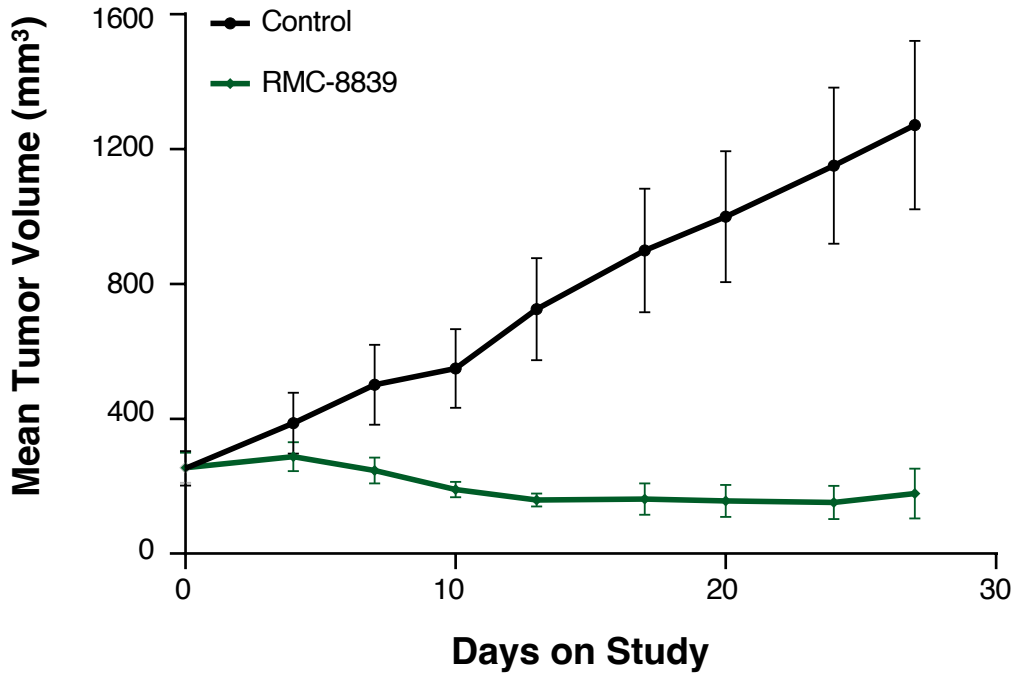
RMC-0708

$KRAS^{Q61H}$ NSCLC[1]



RMC-8839

$KRAS^{G13C}$ NSCLC[2]



Revolution Medicines preclinical research.

1. RMC-0708 dosed at 30 mg/kg PO QD, n=5/group; RMC-8839 dosed at 100 mg/kg PO QD; n=5/group.
2. HCC2108 subcutaneous xenograft model (NSCLC, $KRAS^{Q61H/Q61H}$); ST2822B subcutaneous xenograft model (NSCLC, $KRAS^{G13C/WT}$).

Complementary RAS(ON) Inhibitors Designed for Monotherapy and Combination Strategies Against RAS-Addicted Cancers

RAS^{MULTI} Inhibitor

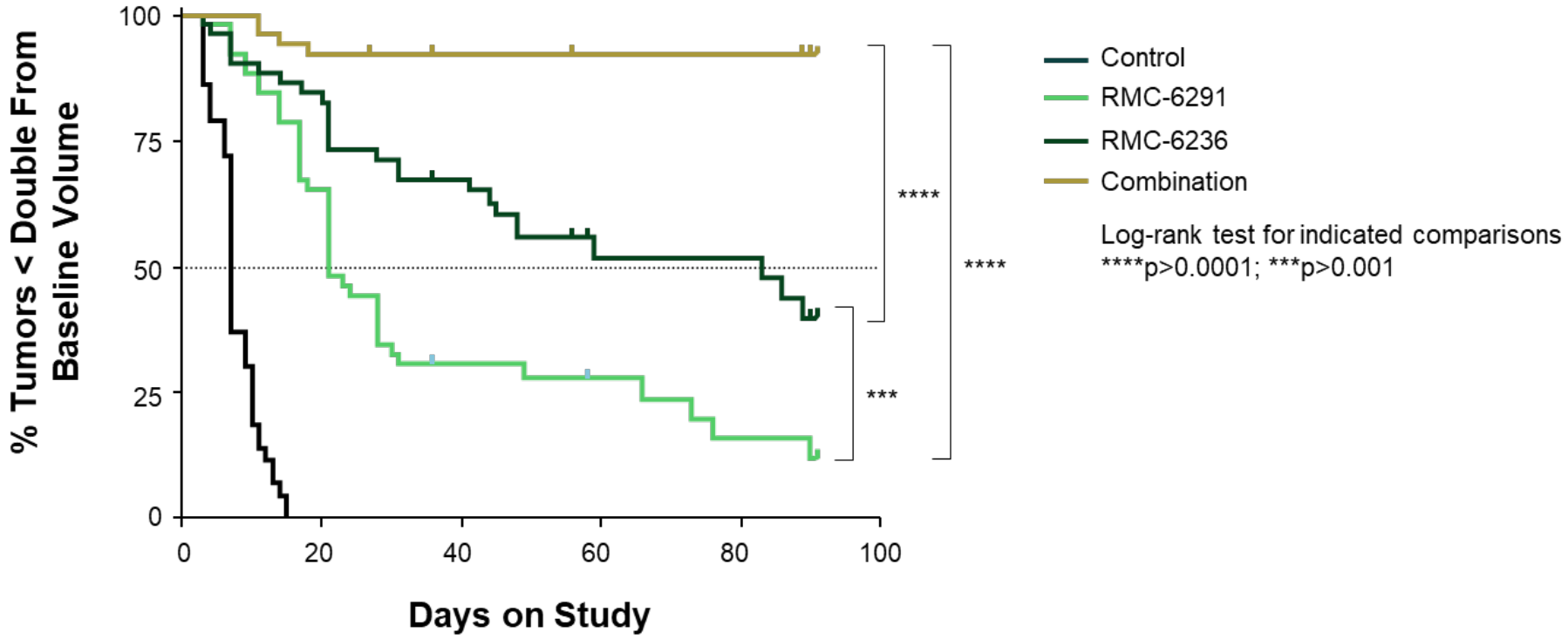
- Monotherapy with broad potential for RAS-addicted cancers
- Core of RAS(ON) inhibitor doublets with mutant-selective RAS(ON) Inhibitors
- Targeted agent for SOC combinations, including immunologic agents

RAS-Mutant Selective Inhibitor

- Alternative monotherapy approaches
- Complementary to RAS^{MULTI} inhibitor in RAS(ON) inhibitor doublets
- Differentiated targeted agent profiles for SOC combinations, including immunologic agents

SOC, standard of care.

RMC-6236 + RMC-6291 Doublet Overcomes Resistance and Prolongs Durability in KRAS^{G12C} NSCLC Models



- RAS(ON) inhibitor doublet has been evaluated across seven models, including five identified as resistant to RMC-6291 monotherapy

Revolution Medicines preclinical research.
RMC-6236 dosed at 25 mg/kg PO QD (n=52); RMC-6291 dosed at 100 or 200 mg/kg PO QD (n=52); combination (n=51).

Summary

RMC-6236, clinical stage, RAS^{MULTI}

- Targets a broad array of RAS mutations, as well as wild-type RAS
- Tumor regressions at well-tolerated doses in preclinical models
- Preclinical modelling predicted tumor regressions at doses starting around 80 mg in humans

RMC-6291, clinical stage, covalent $KRAS^{G12C}$ selective inhibitor

- Highly potent preclinically against $KRAS^{G12C}$-mutant tumors across a wide range of dose levels and histologies
- Unique mechanism of action targets tumors with resistance to $KRAS^{G12C}$(OFF) inhibitors

RMC-9805, clinical stage, covalent $KRAS^{G12D}$ selective inhibitor

- Highly potent preclinically against $KRAS^{G12D}$-mutant tumors across dose levels and histologies

- Additional mutant-selective RAS(ON) inhibitors progressing in development target $KRAS^{G12V}$ (RMC-5127), $KRAS^{Q61H}$ (RMC-0708), and $KRAS^{G13C}$ (RMC-8839)

- Combinations of mutant-selective inhibitors with RAS^{MULTI} have potential to increase potency and overcome emergent resistance

Acknowledgements

Thanks to all the patients who participated in Revolution Medicines studies, their families who supported them, and the clinical investigators and research staff who cared for them.

Revolutions Medicines Clinical and Preclinical Teams