AACR American Association for Cancer Research®
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10
#AACR24
AACR.ORG/AACR24

RMC-6236, a RAS(ON) Multi-Selective Tri-Complex Inhibitor

Elena Koltun, Ph.D., VP, Medicinal Chemistry
Revolution Medicines, Inc.
Redwood City, California

Wei Lin, MD, Chief Medical Officer
Revolution Medicines, Inc.
Redwood City, California

Revolution Medicines

Disclosure Information

Elena Koltun

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

Wei Lin

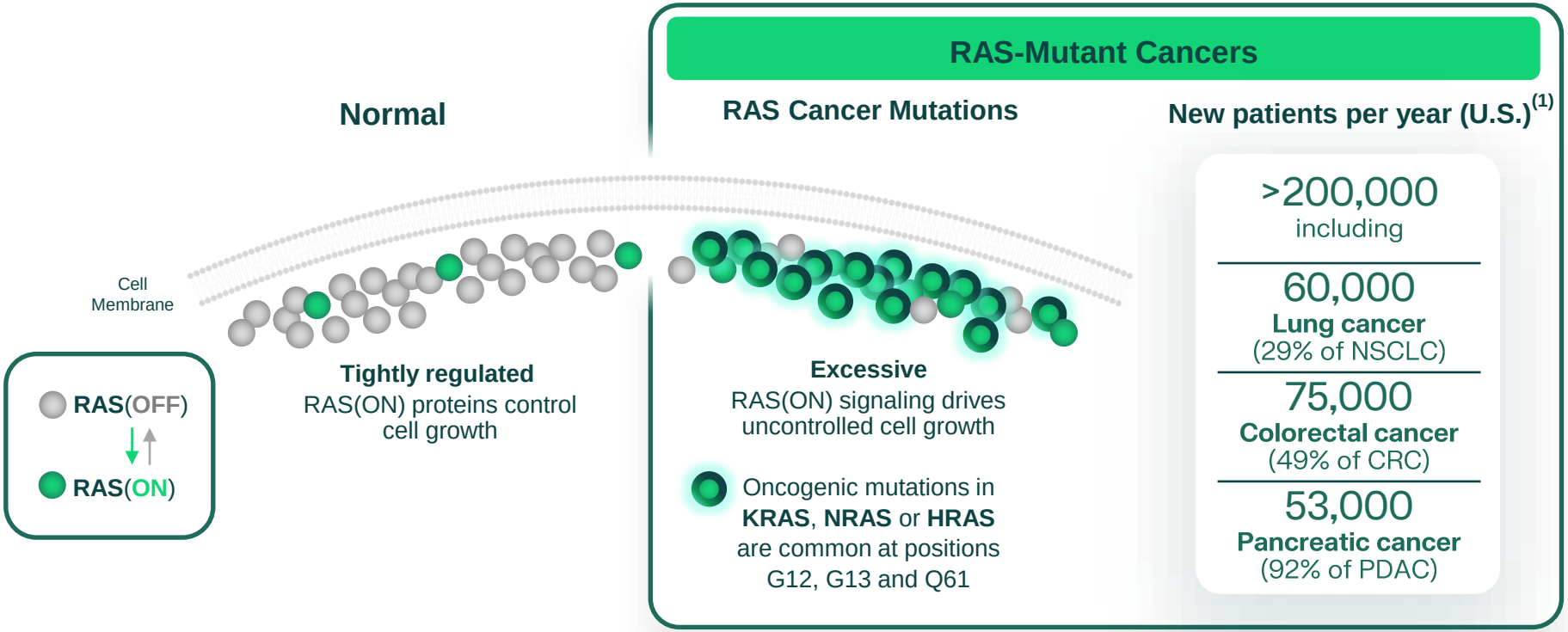
I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

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

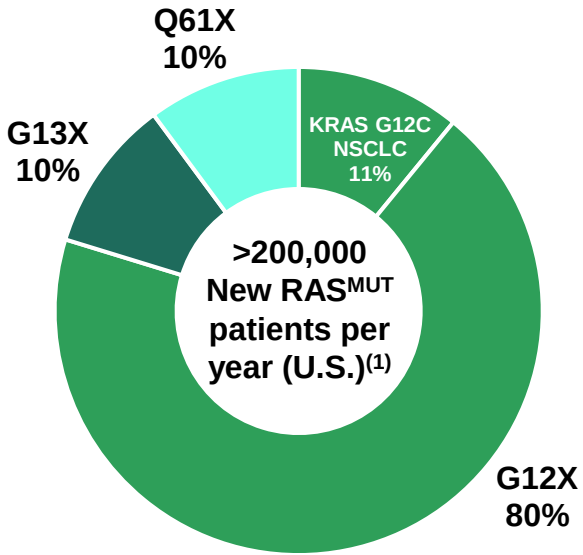
AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24



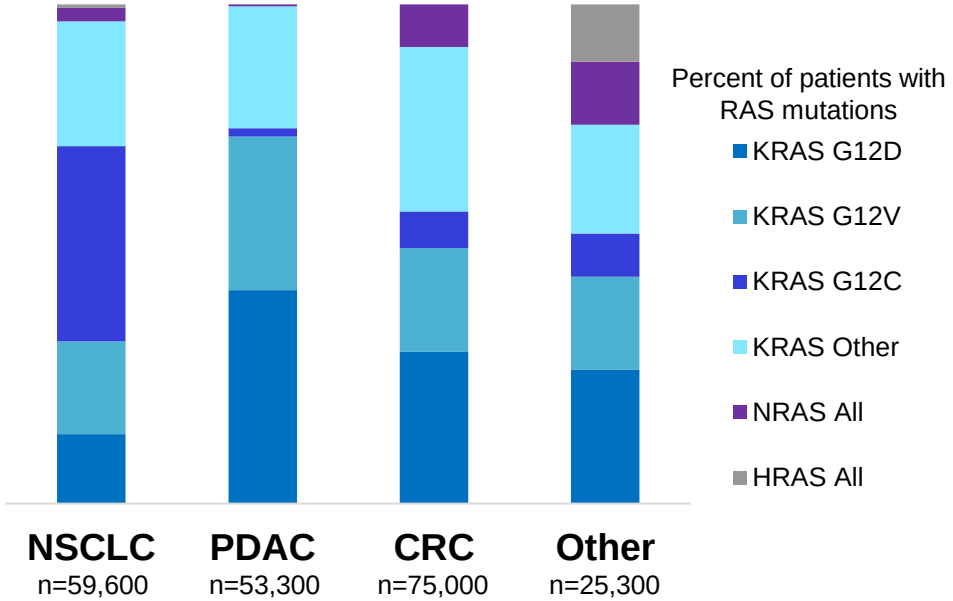
(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023

Large Unmet Needs Across RAS-Mutant Cancers with Diverse Driver Mutations Beyond KRAS^{G12C}

Distribution of Hotspot RAS Mutations Across Solid Tumors(1)

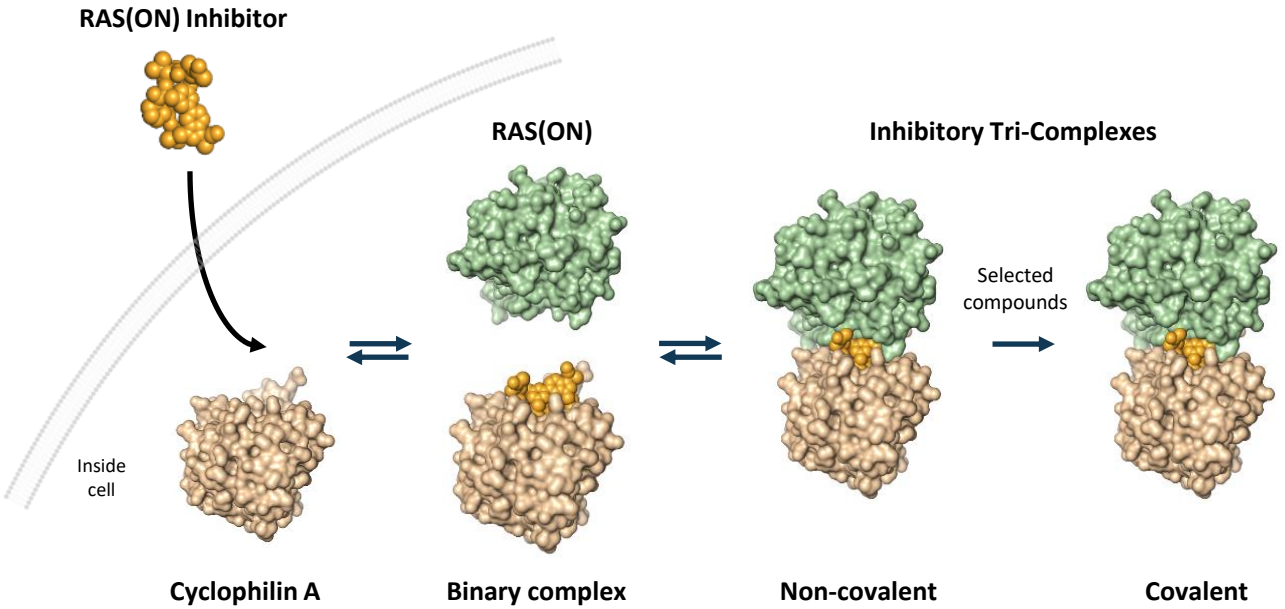


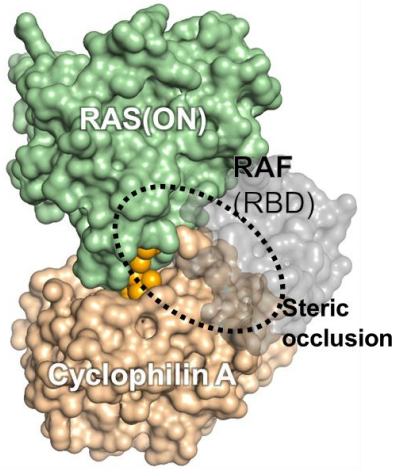
RAS Mutational Landscape Across Solid Tumors(1)



(1) Percentages estimated based on frequencies of KRAS, NRAS, and HRAS mutations in codons G12X, G13X, and Q61X across solid tumors from Foundation Medicine Insights March 2022 and total incidence from ACS Cancer Facts and Figures 2023

Tri-Complex Platform Enables Selective Targeting of Oncogenic RAS(ON) Proteins

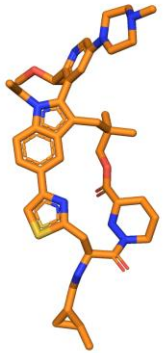


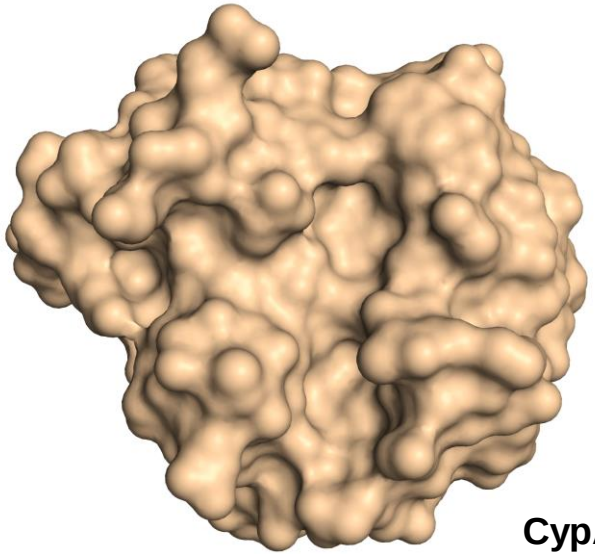


Layered structural model

Chemical Remodeling of Surface of Cyclophilin A by Ligand Promotes Protein-Protein Interactions with RAS(ON)

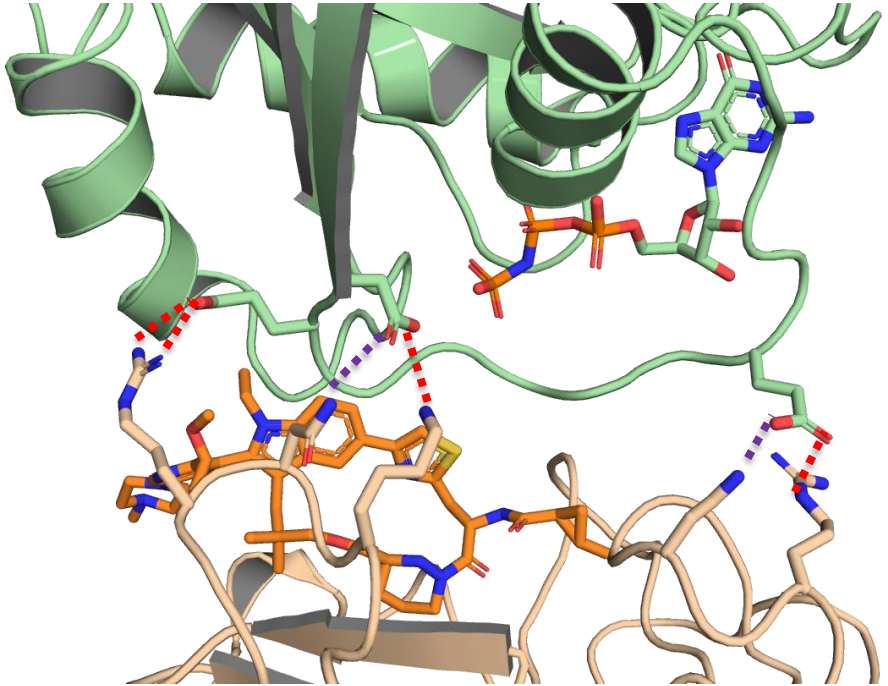
AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24





CypA

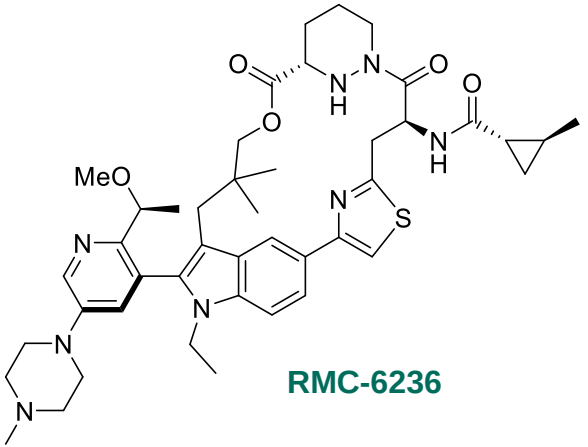
Tri-Complex of KRAS^{G12V}(ON), Ligand, and CypA



H-bond Salt Bridge

RMC-6236, an Oral RAS(ON) Multi-Selective Tri-Complex Inhibitor

ID	RMC-6236
pERK, (RAS-dependent, IC_{50}, nM)[a]	0.4-3
CTG, (RAS-dependent, IC_{50}, nM)	1-27
Selectivity over RAS-independent cells[b]	>1,000X
Off-target safety panel	Low Risk
Average %F oral bioavailability (x-species)	29
Met Clearance (hepatocytes, multiple species)	Low to Moderate

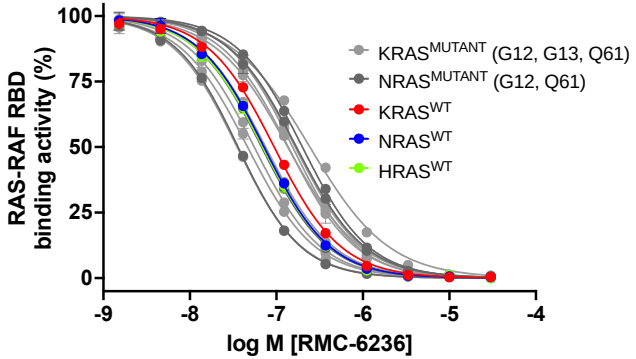


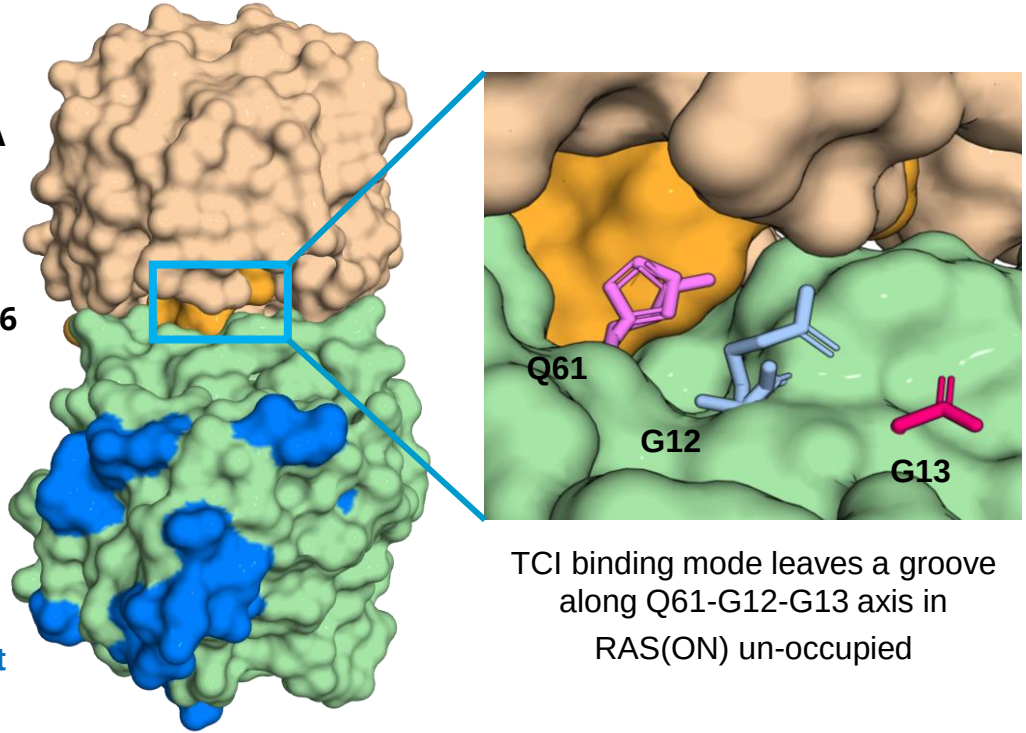
RMC-6236

a: Range reflects sensitivities across multiple RAS-variant cell lines
b: Ratio based on cell growth assays with cell line bearing $KRAS^{G12V}$ mutation

Tri-Complex Inhibitor Binding Mode Enables Broad Spectrum RAS(ON) Activity

Biochemical RAS-RAF RBD Disruption



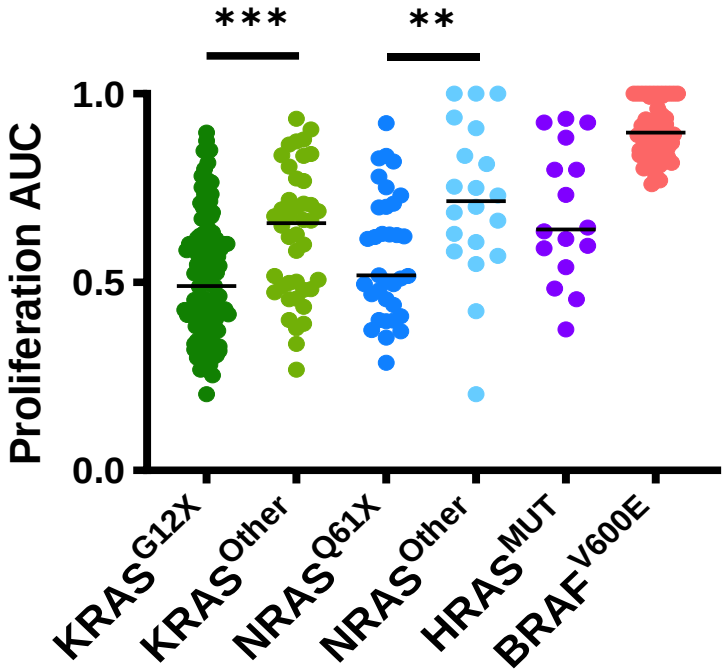


TCI binding mode leaves a groove along Q61-G12-G13 axis in RAS(ON) un-occupied

RAS Mutant Cell Lines Are Highly Sensitive to RAS(ON) Multi-Selective Inhibition

Sensitivity to RMC-6236 by Mutated *RAS* Codon

Increasing Sensitivity to RMC-6236



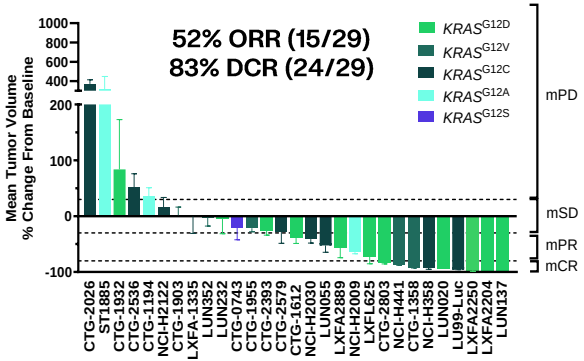
**p < 0.01, ***p < 0.001
by Wilcoxon rank-sum test with continuity correction

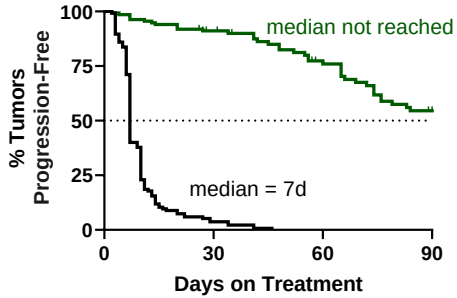
PRISM screening data generated in collaboration with Andy Aguirre and Broad PRISM

RMC-6236 Drives Durable Responses and is Well-Tolerated in Models of Major Human Cancers with RAS^{G12X} Drivers

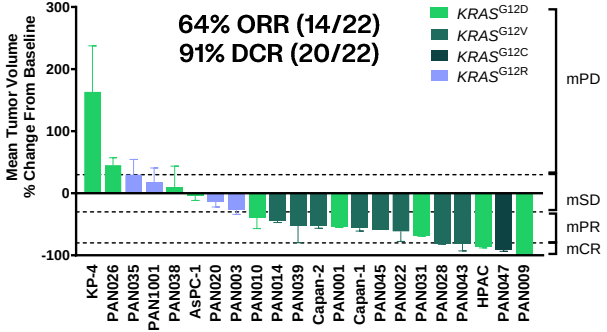
AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

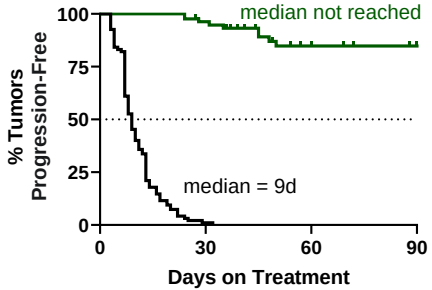
NSCLC



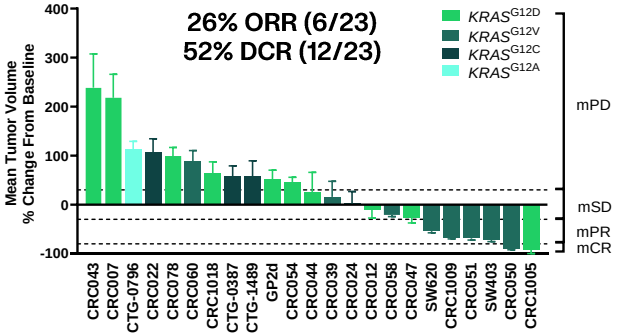


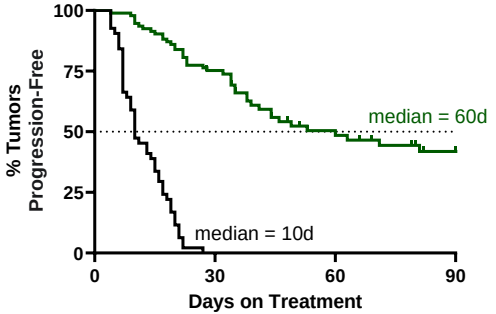
PDAC





CRC





Control — RMC-6236

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

Probing Breadth of Activity of RMC-6236 in RAS-Addicted Solid Tumors

Beyond KRAS G12 mutations
Beyond NSCLC and PDAC

Revolution Medicines

RMC-6236: Treatment-Related Adverse Events

Patients with NSCLC and PDAC Treated at ≥80 mg QD (N = 111)					
Maximum severity of TRAEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash*	58 (52)	25 (23)	7 (6)	0	90 (81)
Nausea	40 (36)	11 (10)	0	0	51 (46)
Diarrhea	28 (25)	14 (13)	1 (1)	0	43 (39)
Vomiting	30 (27)	7 (6)	0	0	37 (33)
Stomatitis	13 (12)	9 (8)	2 (2)	0	24 (22)
Fatigue	11 (10)	6 (5)	0	0	17 (15)
Other select TRAEs, n (%)					
ALT elevation	8 (7)	1 (1)	0	0	9 (8)
AST elevation	8 (7)	0	0	0	8 (7)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction, n (%)**	0	10 (9)	5 (5)†	0	15 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)‡	1 (1)

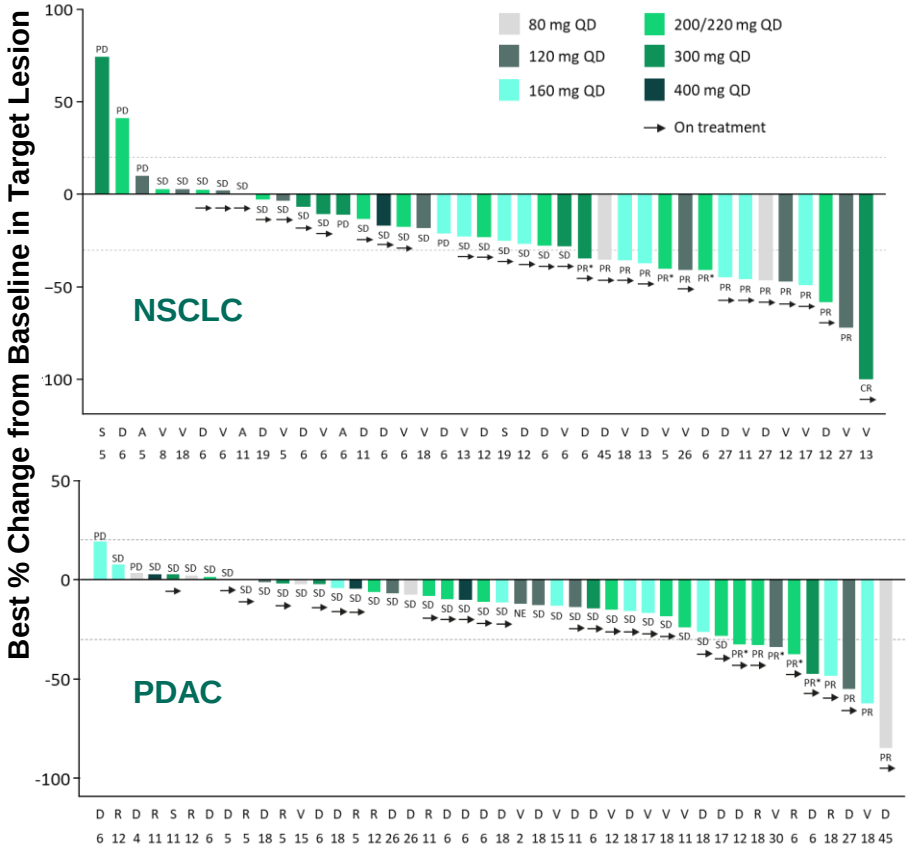
- Median duration of treatment: 2.1 months (range: 0.2–10.9) (at time of data extraction)
- No fatal TRAEs were observed.

Data Extracted 12 Oct 2023
Arbour et al. ESMO 2023

*Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema, rash erythematous; multiple types of rash may have occurred in the same patient
**The most common TRAE leading to dose reduction was rash.
†Grade 3 TRAEs leading to reduction were rash (n = 4), including one patient with a dose reduction due to rash and decreased appetite, and stomatitis (n = 1).
‡One Grade 4 TRAE occurred in a patient with PDAC at the 80 mg dose level who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment.

RMC-6236: Clinically Active in KRAS G12X NSCLC and PDAC

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24



Data Extracted 12 Oct 2023
Arbour et al. Presented at ESMO 2023

KRAS G12X NSCLC (N=40) [1, 2]	
ORR	**38%**
DCR	**85%**
SOC Benchmark, Docetaxel[3]	
ORR	13%
DCR	60%

KRAS G12X PDAC (N=46) [1, 2]	
ORR	**20%**
DCR	**87%**
SOC Benchmark, GnP[3]	
ORR	11%
DCR	56%

(1) Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.
(2) Tumor response per RECIST 1.1.
(3) Docetaxel efficacy from CodeBreaK 200, Lancet (2023) 401: 733-746.
GnP=Gemcitabine plus nab-paclitaxel; GnP efficacy from Br J Cancer (2022) 126:1394-1400.

RMC-6236: CR in KRAS G12D PDAC Patient Exemplifies Deep Responses Observed Since ESMO 2023

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Corrected

Baseline Characteristics

77-year-old woman

Diagnosed with Stage IV PDAC in 2023

Treatment History

Prior therapy: FOLFIRINOX

RMC-6236 Treatment Course

C1D1: Started at 300 mg QD

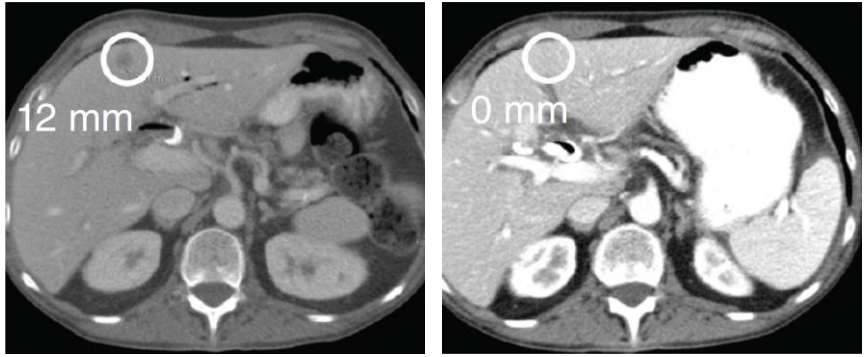
C3D1: Partial response

C5D1: Complete response

C7D1: Confirmed complete response

Data Extract: 5 April 2024

Baseline **Week 12**



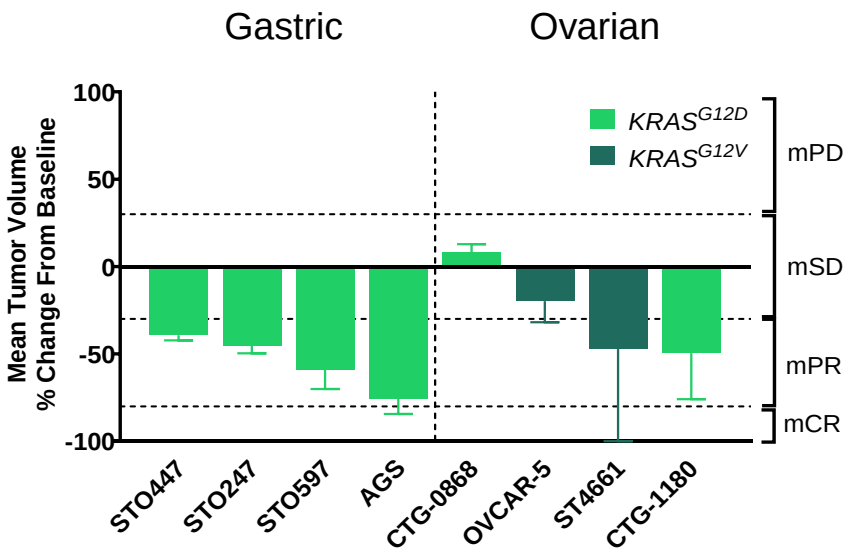
Target Lesion: Liver Metastasis

Target Lesion	Baseline (mm)	Week 12 (mm)
1. Liver	12	0
2. Liver	10	0
Sum of Diameters	**22**	**0 (-100%)**
Overall Response	**-**	**CR**

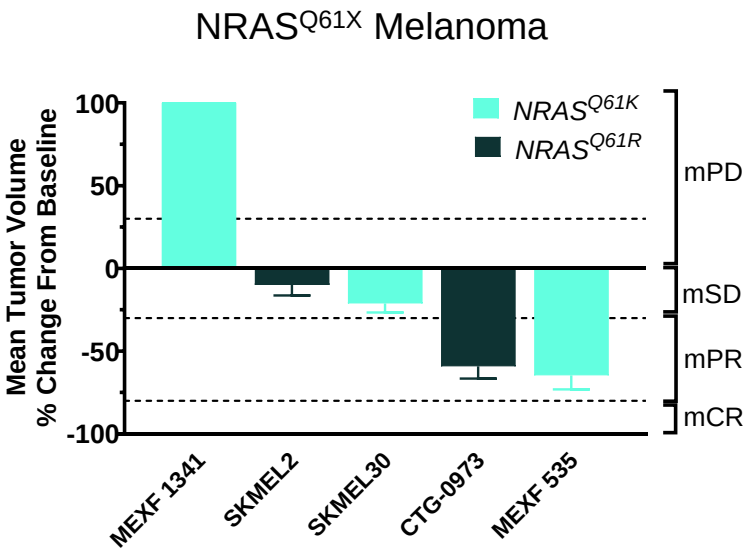
RMC-6236 is Highly Active in RAS-Driven Tumor Models Beyond PDAC and NSCLC, and Beyond KRAS^{G12X} Mutations

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Tumor Types Beyond PDAC and NSCLC



Mutations Beyond KRAS G12X



RMC-6236: KRAS Q61H PDAC Case Exemplifies Responses Beyond KRAS G12X

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Baseline Characteristics

80-year-old man

Diagnosed with stage I PDAC in 2022

Received neoadjuvant chemotherapy followed by pancreaticoduodenectomy

Treatment History

Prior therapies:

Gemcitabine + Nab-paclitaxel

RMC-6236 Treatment Course

C1D1: Started at 300 mg QD

Dose reduced to 200 mg QD (grade 2 acneiform rash)

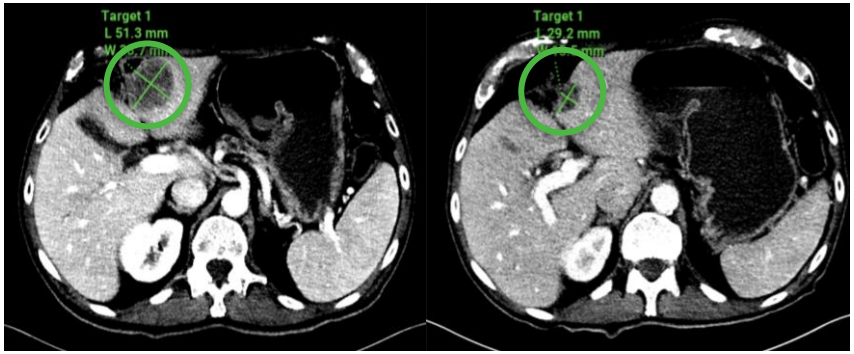
Dose reduced to 120 mg (grade 3 palmar plantar erythrodysesthesia [PPE] or hand and foot syndrome)

C3D1: Partial response

C5D1: Confirmed partial response

Data Extract: 5 April 2024

Baseline **Week 12**



Target Lesion: Liver (segment 3)

Target Lesion	Baseline (mm)	Week 12 (mm)
1. Liver (segment 3)	51.3	29.2
2. Liver (segment 7)	37.3	20.5
3. Adrenal gland (left)	21.1	9.6
Sum of Diameters	109.7	**59.3 (-45.9%)**
Overall Response	-	**PR**

RMC-6236: NRAS Q61K Melanoma Case Exemplifies Responses in Broader Genotypes and Tumor Types

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Baseline Characteristics

63-year-old man

Diagnosed with stage IV melanoma in 2022

Treatment History

Prior therapies: Nivolumab + Ipilimumab
Nivolumab + Relatlimab
Ipilimumab

RMC-6236 Treatment Course

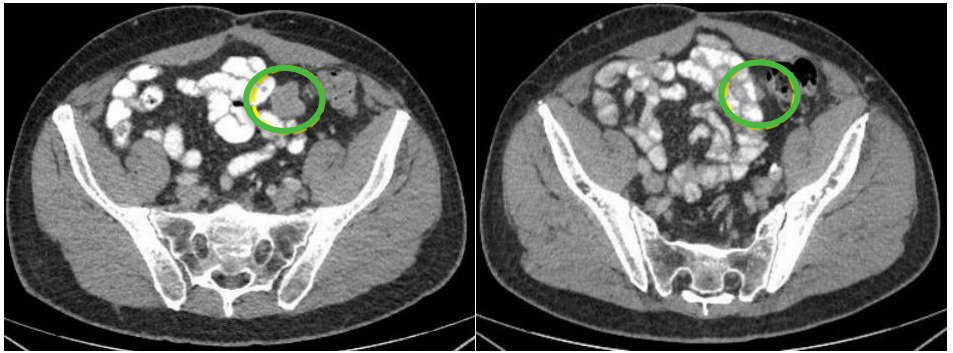
C1D1: Started at 300 mg QD

C3D1: Partial response

C5D1: Complete response

Data Extract: 5 April 2024

Baseline **Week 6**



Target Lesion: Stomach (abdominal peritoneum/omentum left)

Target Lesion	Baseline (mm)	Week 12 (mm)
Stomach	28.8	0
Sum of Diameters	28.8	**0 (-100%)**
Overall Response	-	**CR**

RMC-6236: BRAF V600E CRC Response in Presence of Multiple RAS-Mediated Resistance Mechanisms

AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

Baseline Characteristics

61-year-old woman

Diagnosed with stage IV BRAF V600E CRC in 2022 with metastasis occupying 40% of the liver

Following treatment with encorafenib + cetuximab, ctDNA showed BRAF V600E, and newly acquired KRAS G12V, NRAS G13R, NRAS Q61R mutations

Treatment History

Prior therapies: FOLFIRI + Bevacizumab
Encorafenib + Cetuximab
Encorafenib + Cetuximab + Nivolumab

RMC-6236 Treatment Course

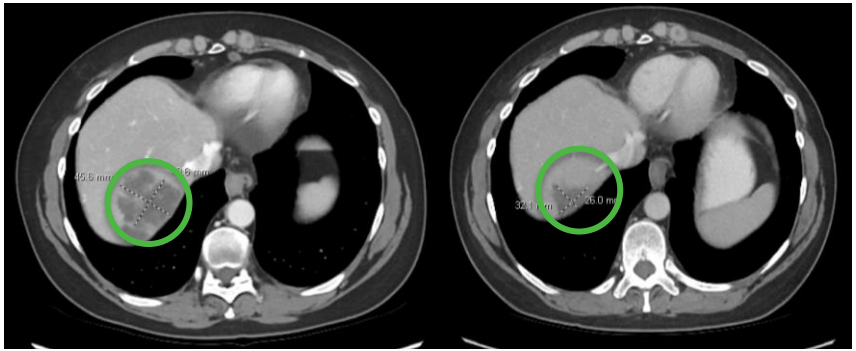
C1D1: Started at 300mg QD
Dose reduced to 200mg (grade 2 mucositis)

C3D1: Partial response

C5D1: Confirmed partial response

Data Extract: 5 April 2024

Baseline **Week 6**



Target Lesion: Liver (segment VII)

Target Lesion	Baseline (mm)	Week 12 (mm)
1. Skin (subcutaneous nodule)	21	0
2. Liver (segment VII)	46	32
3. Liver (segment IV)	45	35
4. Lymph nodes	17	11
Sum of Diameters	129	**78 (-39.5%)**
Overall Response	-	**PR**

Summary

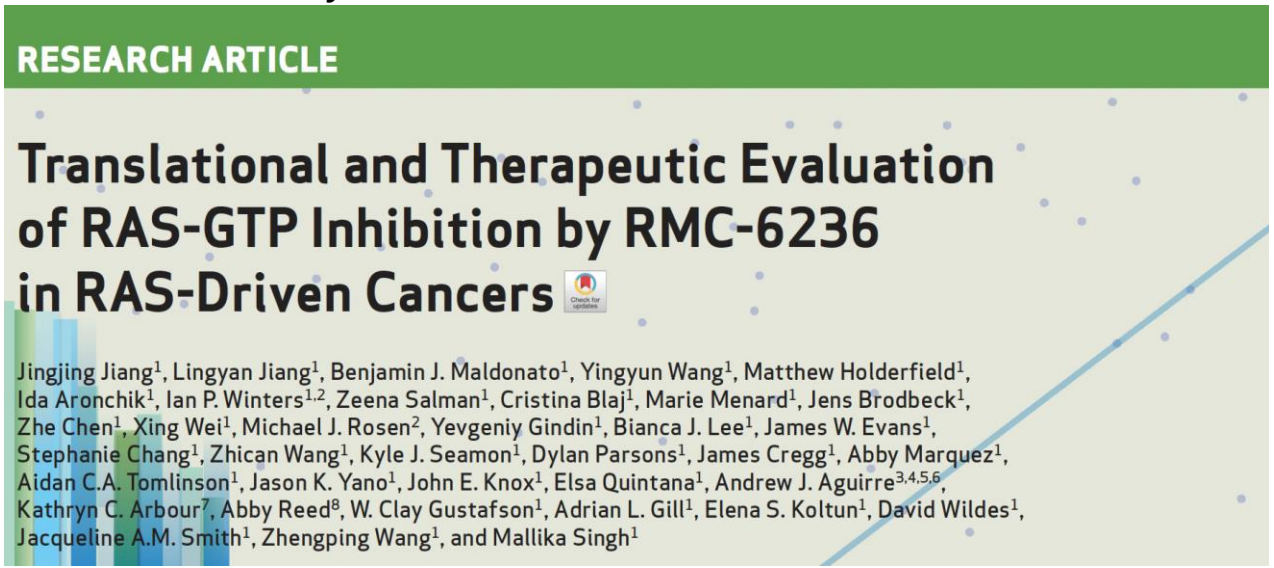
- RMC-6236 is the first investigational orally bioavailable, RAS(ON) multi-selective tri-complex inhibitor
- Preclinically, broad RAS(ON) inhibition via RMC-6236 is well tolerated and drives profound anti-tumor activity across diverse models of RAS-addicted cancers
- Clinically, RMC-6236 was previously reported (ESMO 2023) to be well-tolerated and to show encouraging anti-tumor activity in patients with previously treated advanced NSCLC or PDAC harboring common KRAS G12 mutations, including G12D, G12V, and G12R. Complete responses to monotherapy have been observed
- Consistent with preclinical observations, RMC-6236 has shown clinical activity in solid tumors beyond NSCLC and PDAC, and in tumors harboring KRAS or NRAS mutations beyond G12X including RAS-mediated mechanisms of resistance to a targeted BRAF inhibitor

Acknowledgements

AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

- The patients and investigators who are making clinical evaluation of RMC-6236 possible
- Revolution Medicines Research and Development Teams

Cancer Discovery Simultaneous Publication


RESEARCH ARTICLE

Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers

Jingjing Jiang[1], Lingyan Jiang[1], Benjamin J. Maldonato[1], Yingyun Wang[1], Matthew Holderfield[1], Ida Aronchik[1], Ian P. Winters[1,2], Zeena Salman[1], Cristina Blaj[1], Marie Menard[1], Jens Brodbeck[1], Zhe Chen[1], Xing Wei[1], Michael J. Rosen[2], Yevgeniy Gindin[1], Bianca J. Lee[1], James W. Evans[1], Stephanie Chang[1], Zhican Wang[1], Kyle J. Seamon[1], Dylan Parsons[1], James Cregg[1], Abby Marquez[1], Aidan C.A. Tomlinson[1], Jason K. Yano[1], John E. Knox[1], Elsa Quintana[1], Andrew J. Aguirre[3,4,5,6], Kathryn C. Arbour[7], Abby Reed[8], W. Clay Gustafson[1], Adrian L. Gill[1], Elena S. Koltun[1], David Wildes[1], Jacqueline A.M. Smith[1], Zhengping Wang[1], and Mallika Singh[1]

Scan QR code to access the full work online

AACR JOURNALS