Targeting RAS-Addicted Cancers with Investigational RAS(ON) Inhibitors

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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(ON) proteins control cell growth

Tightly regulated

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)


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)

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

<table>
<thead>
<tr>
<th>MULTI</th>
<th>RAS Selectivity</th>
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<td>RMC-6236</td>
<td>Clinical</td>
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<td>RMC-6291</td>
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<td>RMC-9805</td>
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<td>RMC-5127</td>
<td>IND-enabling</td>
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<tr>
<td>RMC-0708</td>
<td>IND-enabling</td>
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<tr>
<td>RMC-8839</td>
<td>IND-enabling</td>
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IND, investigational new drug.

>200,000 New RAS cancer patients/year (US)
166,000 New KRAS$^{G12X}$ patients per year (US)*

CRC 31%
NSCLC 30%
PDAC 29%
Other 10%

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

Three Mutational Hotspots in RAS

Biochemical (TR-FRET)

K, H, NRAS divergent residues

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<sup>G12V/WT</sup>; 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.

Mouse exposure of 10 mg/kg is equivalent to the projected 80 mg human dose.
**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**

- 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.

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<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Dose Expansion / Optimization</th>
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<tbody>
<tr>
<td>10 mg</td>
<td>Lowest dose projected to induce tumor regressions in human xenograft models with KRAS(^{G12X}) mutations in mice(^1)</td>
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<tr>
<td>20 mg</td>
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<td>40 mg</td>
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<td>400 mg</td>
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<td>500 mg</td>
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RMC-6291: Clinical Stage, Mutant-Selective, Covalent RAS(ON) Inhibitor with Best-in-Class Potential for KRAS$^{G12C}$ Cancers

**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

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**Preclinical Profile**

- **CRC**: 17%
- **PDAC**: 3%
- **Other**: 7%
- **NSCLC**: 73%

32,000 New KRAS$^{G12C}$ patients per year (US)*

*New patients per year rounded to nearest 1000.*
RMC-6291 Drives Tumor Regressions at Low Doses in Preclinical Models of KRAS\textsuperscript{G12C}–Mutant NSCLC

Revolution Medicines preclinical research. NCI-H358 CDX (NSCLC, KRAS\textsuperscript{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)

- RMC-6291
- Sotorasib
- Adagrasib

Rapid KRAS\textsuperscript{G12C} Covalent Modification (in Vivo, Tumor)

- Adagrasib 100 mg/kg
- RMC-6291 100 mg/kg
- RMC-6291 10 mg/kg

Insensitivity to Non-Genomic and Genomic Mechanisms of Resistance

- NCI-H358, HGF
- LU65, HGF
- LU65, EGF

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

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$^{G12C/WT}$, ERBB3$^{amp}$, KRAS$^{amp}$); RMC-6291 dosed at 200 mg/kg PO QD; adagrasib dosed at 100 mg/kg PO QD.

Revolution Medicines preclinical research.

AACR-NCI-EORTC INTERNATIONAL CONFERENCE: MOLECULAR TARGETS AND CANCER THERAPEUTICS
**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

### Dose Escalation

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

- 400 mg BID
- 300 mg BID
- 200 mg BID
- 100 mg BID

### Dose Expansion / Optimization

- 200 mg QD
- 100 mg QD
- 50 mg QD

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).

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

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

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

<table>
<thead>
<tr>
<th>KRAS:</th>
<th>WT</th>
<th>G12D</th>
<th>G13D</th>
<th>G12C</th>
<th>G13C</th>
</tr>
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<tbody>
<tr>
<td>X-linked KRAS</td>
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<td>KRAS H/NRAS</td>
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**61,000**

New KRAS\(^{G12D}\) patients per year (US)*

- **CRC** 38%
- **NSCLC** 14%
- **PDAC** 37%
- **Other** 11%

**Mean Tumor Volume % Change from Baseline**

- PDAC (n=9)
- NSCLC (n=9)
- CRC (n=7)

*New patients per year rounded to nearest 1000.*
**RMC-5127: First-in-Class Mutant-Selective RAS(ON) Inhibitor for KRAS\textsuperscript{G12V}-Mutant Cancers**

**In Vivo Anti-Tumor Activity Across KRAS\textsuperscript{G12V} Cancer Models**

- **CRC** 33%
- **NSCLC** 23%
- **PDAC** 34%
- **Other** 10%

**48,000**
New KRAS\textsuperscript{G12V} patients per year (US)*

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

*New patients per year rounded to nearest 1000.
mCR, molecular complete response; mPR, molecular partial response; mSD, molecular stable disease.
First-in-Class Mutant-Selective RAS(ON) Inhibitors Targeting KRAS^{Q61H} and KRAS^{G13C} Cancers

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

<table>
<thead>
<tr>
<th>RAS\textsuperscript{MULTI} Inhibitor</th>
<th>RAS-Mutant Selective Inhibitor</th>
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<tr>
<td>• Monotherapy with broad potential for RAS-addicted cancers</td>
<td>• Alternative monotherapy approaches</td>
</tr>
<tr>
<td>• Core of RAS(ON) inhibitor doublets with mutant-selective RAS(ON) Inhibitors</td>
<td>• Complementary to RAS\textsuperscript{MULTI} inhibitor in RAS(ON) inhibitor doublets</td>
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<tr>
<td>• Targeted agent for SOC combinations, including immunologic agents</td>
<td>• Differentiated targeted agent profiles for SOC combinations, including immunologic agents</td>
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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).
RMC-6236, clinical stage, RAS\textsuperscript{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\textsuperscript{G12C} selective inhibitor

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

RMC-9805, clinical stage, covalent KRAS\textsuperscript{G12D} selective inhibitor

- Highly potent preclinically against KRAS\textsuperscript{G12D}-mutant tumors across dose levels and histologies
- Additional mutant-selective RAS(ON) inhibitors progressing in development target KRAS\textsuperscript{G12V} (RMC-5127), KRAS\textsuperscript{Q61H} (RMC-0708), and KRAS\textsuperscript{G13C} (RMC-8839)
- Combinations of mutant-selective inhibitors with RAS\textsuperscript{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