RMC-6236, a Novel, First in Class, Tri-complex $\text{RAS}^{\text{MULTI}(ON)}$ Inhibitor: Preliminary Clinical Results & Learnings

**Hanson Wade Meeting: RAS-Targeted Drug Development**

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Disclosure Information

• **Research support to institution:** AstraZeneca, BreakThrough Cancer, Celgene/BMS, Eli Lilly, Hale Family Center for Pancreatic Cancer Research, Lustgarten Foundation, NIH/NCI, Novartis, Pancreatic Cancer Action Network, Revolution Medicines, Stand Up to Cancer

• **Paid advisory roles:** Celgene/BMS, GRAIL, Ipsen, Lustgarten Foundation, Mirati, Third Rock Ventures
RMC-6236-001 Trial

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in KRAS

The Christ Hospital Cancer Center, Dana-Farber Cancer Institute, MD Anderson Cancer Center, University of Utah Huntsman Cancer Institute, Memorial Sloan Kettering Cancer Center, NYU Langone Health, Perlmutter Cancer Center, next oncology San Antonio, Virginia
Outline

• Background
• Preclinical data for RMC-6236
• Clinical trial design and initial toxicity and efficacy data for RMC-6236-001 trial
• Future directions for RAS inhibition in pancreatic cancer
KRAS mutant alleles by cancer type

KRAS mutations are most common in the three leading causes of cancer death in US:

NSCLC + PDAC + CRC = 230,170 deaths = 38% of all est. US cancer deaths in 2023

32% NSCLC [76,269 est. new cases in 2023]
92% PDAC [58,926 est. new cases in 2023]
45% CRC [68,400 est. new cases in 2023]

Percent and allele for codon 12 KRAS mutations by cancer type:

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

RAS(OFF)
GDP-loaded

GEFs (e.g. SOS1)

RAS(ON)
GTP-loaded

GAPs (e.g. NF1)

Cell growth and survival effectors

Sotorasib
Adagrasib

Covalent KRAS\textsuperscript{G12C} (OFF) inhibitors

GEFs: Guanine nucleotide exchange factors
GAPs: GTPase activating proteins
Natural Compounds Use Abundant Cellular Chaperones to Form Tri-Complexes with Distinct Biological Targets

This mechanism may be adapted to difficult-to-drug targets like RAS(ON)
Chemical remodeling of a cellular chaperone to target the active state of mutant KRAS

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

Inside cell

RAS(ON) Inhibitor

Cyclophilin A

Binary complex

Non-covalent

Covalent

Inhibitory Tri-Complexes

Selected compounds

Layered structural model

Steric occlusion

RAS(ON)

RAF (RBD)

RMC-6236 RAS\textsuperscript{MULTI}
RMC-0708 KRAS\textsuperscript{Q61H}

RMC-6291 KRAS\textsuperscript{G12C}
RMC-9805 KRAS\textsuperscript{G12D}
RMC-8839 KRAS\textsuperscript{G13C}

Tri-complex with cyclophilin A and mutant or wild-type KRAS, NRAS, and HRAS
KRAS\textsuperscript{G12X} Mutated Cancer Cell Lines are Highly Addicted to KRAS

**Genetic Dependency on KRAS, data from DepMap**

**Inhibition of Proliferation, PRISM screen**

PRISM data generated in collaboration with Dr. Andrew Aguirre (DFCI) and Broad PRISM platform
KRAS Gene effect data acquired from DepMap.org (Public 22Q4, Chronos score)
RAS\textsuperscript{MULTI}(ON) inhibition phenocopies KRAS knockout via CRISPR
RMC-6236: Highly Active with Durable Benefit Across *in Vivo* Models of Major Human Cancers with KRAS\(^{G12X}\) Drivers

RMC-6236 dosed at 25 mg/kg po qd; n=1-10/group
ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival
Progression defined as tumor doubling from baseline. Responses assigned according to mRECIST
NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma; CRC = colorectal cancer
RMC-6236-001 Phase 1/1b Study Design

Key Eligibility Criteria

- Advanced solid tumors with KRAS\textsuperscript{G12} mutations (currently excluding KRAS\textsuperscript{G12C})
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability
- Preliminary anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD

Dose Expansion / Optimization

- Lowest dose/exposure range predicted to drive tumor regressions in patients based on preclinical models
RMC-6236-001: Treatment-Related AEs Occurring in ≥10% of All Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>10 mg QD (N=3)</th>
<th>20 mg QD (N=13)</th>
<th>40 mg QD (N=9)</th>
<th>80 mg QD (N=7)</th>
<th>120 mg QD (N=4)</th>
<th>Overall (N=36)</th>
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<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
<td>Grade ≥3</td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Rash (CMQ)*</td>
<td>0 (33.3%)</td>
<td>0</td>
<td>2 (15.4%)</td>
<td>0</td>
<td>4 (44.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>2 (15.4%)</td>
<td>0</td>
<td>6 (66.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>0</td>
<td>2 (22.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (22.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>0</td>
<td>2 (22.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

One related grade 4 adverse event of bowel perforation (also considered a serious adverse event) was reported in a patient receiving 80 mg daily. The likely cause of the perforation was considered to be shrinkage of metastatic KRAS<sub>G12V</sub> pancreatic cancer at the site of full-thickness bowel infiltration.

EDC data as of 02/17/2023. CMQ = Customized MedDRA Query
*Consists of dermatitis acneiform, dermatitis psoriasiform, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, and rash pustular.
RMC-6236-001: Change in Tumor Burden from Patients with KRAS$^{G12X}$ NSCLC or Pancreatic Cancer Treated at $\geq 40$ mg Daily

Most recent scan: C3D1 C3D1 C5D1 C3D1 C7D1 C3D1 C7D1 C3D1 C3D1 C3D1 C3D1 C3D1 C5D1 C5D1

EDC data as of 02/17/2023; efficacy evaluable patients defined as those in this data set with at least one post baseline response assessment or who have died or have experienced clinical progression prior to the first post baseline scan (n=12). Cycle time is 21 days. SD = stable disease, PR = partial response. NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma. *PR subsequently confirmed as of 03/16/23.
RMC-6236-001 Case Report: Patient with KRAS$^{G12V}$ Metastatic Pancreatic Cancer

- 52 year-old male
- Pancreas mass and peritoneal metastases identified October 2022
- Biopsy of peritoneal nodule: pancreatic adenocarcinoma
- Oct-2022 to Apr-2023 Gemcitabine/Nab-paclitaxel + investigational agent: Stable disease x 6 months
- Apr-2023 to May-2023 5-fluorouracil / folinic acid / nanoliposomal irinotecan: Progressive disease

- Progression of peritoneal metastases
- Somatic NGS: KRAS$^{G12V}$ with co-occurring TP53 and SMAD4 mutations from peritoneal biopsy
- Treated with RMC-6236 at 160 mg daily (dose level 6)
- Partial response identified at 6 weeks (RECISTv1.1, -35%), which is ongoing after 4 months
- Normalization of serum CA19-9
- Grade 1 rash, nausea, and diarrhea

Data as of 09/21/2023
Case Report: Confirmed Partial Response by CT imaging

Peritoneal Disease

Baseline

On Treatment

RMC-6236, C5D1

SLD = sum of longest diameters per RECIST 1.1

Images courtesy of RMC-6236-001 study site with additional annotation by RVMD
(SLD values and red arrows highlighting detectable lesions)

SLD: 65.9 mm

SLD: 24.9 mm

Partial Response: -62%

Data as of 09/21/2023
Further data in PDAC, NSCLC, and other histologies to be presented at...

AACR-NCI-EORTC INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 11-15, 2023
Oral Presentation
Alex Spira, MD

Preliminary safety and pharmacokinetic profiles of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS\textsuperscript{MULTI(ON)} inhibitor in patients with KRAS mutant solid tumors on the Phase 1 trial RMC-6236-001

ESMO Congress

October 20-24, 2023
Oral Presentation
Kathryn Arbour, MD

Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC)
Pancreatic Cancer Survival

AJCC Stage

1. Localized: 60%
2. Locally Advanced: 15%
3. Metastatic: <5%
4. Metastatic: <1%

5-Year Survival (%)
Pancreatic Cancer Survival

AJCC Stage

Located

Locally Advanced

Metastatic

5-Year Survival (%) 100 75 50 25 5 100%

<1%

20%

25%

55%

60%

15%

<5%

<1%

Chemotherapy

Peri-operative chemotherapy

Median Survival < 1 year

High Recurrence Rate

AJCC Stage 1 2 3 4

Localized Locally Advanced Metastatic
Current treatment paradigm for metastatic pancreatic cancer

Metastatic PDAC

1st Line Treatment

* NALIRIFOX

* FOLFIRINOX

* Gemcitabine / Nab-paclitaxel

2nd Line Treatment

Gemcitabine / Nab-paclitaxel

* Gemcitabine / Nab-paclitaxel

* 5FU/LV/nal-Iri

* FOLFIRI

* FOLFOX

* FOLFIRINOX

* Molecularly selected therapies (when possible)

MMR-D: Anti-PD-1 Ab
gBRCA1/2 mut: Olaparib
Other targets: BRAF mut, fusions

* Randomized phase 3 data

All patients:
- Germline panel testing
- MMR/MSI testing
- Somatic NGS

5-Fluorouracil, folinic acid, irinotecan, oxaliplatin (Port, Steroids, G-CSF, GI Tox)
For the 1%: KRAS\textsuperscript{G12C} inhibitors in pancreatic cancer

\textbf{Sotorasib in advanced, previously-treated PDAC}

- N=38 patients
- ORR: 21% (8/38)
- DCR: 84% (32/38)
- mPFS: 4.0 mos
- mOS: 6.9 mos

\textbf{Adagrasib in advanced, previously-treated PDAC}

- N=21 patients
- ORR: 33% (7/21)
- DCR: 81% (17/21)
- mPFS: 5.4 mos
- mOS: 8.0 mos

\textbf{Divarasib in advanced, previously-treated PDAC:}

- ORR 43% (3/7); DCR 100% (7/7)

Strickler et al. NEJM 2023

Bekaii-Saab et al. JCO 2023

Sacher et al. NEJM 2023
Evaluating new therapies in metastatic pancreatic cancer

1st Line Treatment

- Chemotherapy
- Chemotherapy + IP
- IP alone

Standard Rx:
mOS: 9-12 mo.
mPFS: 6-7 mo.
RR: 30-40%

Maintenance Chemo

Maintenance IP

IP = Investigational Product
Evaluating new therapies in metastatic pancreatic cancer

1\textsuperscript{st} Line Treatment \rightarrow \textless 50\% \text{ of pts} \rightarrow 2\textsuperscript{nd} Line Treatment

- Chemotherapy
- Chemotherapy + IP
- IP alone

- Chemotherapy
  - Maintenance Chemo
  - Maintenance IP

- Standard Rx: mOS: 9-12 mo. mPFS: 6-7 mo. RR: <10\%

- Chemotherapy + IP
- IP alone

- Standard Rx: mOS: 6 mo. mPFS: 3 mo. RR: 30-40\%

\textbf{IP = Investigational Product}
Evaluating new therapies in metastatic pancreatic cancer

1st Line Treatment

- Chemotherapy
- Chemotherapy + IP
- IP alone
- Standard Rx: mOS: 9-12 mo. mPFS: 6-7 mo. RR: 30-40%

2nd Line Treatment

- Chemotherapy
- Chemotherapy + IP
- IP alone
- IP = Investigational Product
- Standard Rx: mOS: ? mo. mPFS: ? mo. RR: <5%

3rd Line Treatment

- IP alone
- Few pts

Maintenance Chemo

- Maintenance IP
- Standard Rx: mOS: 6 mo. mPFS: 3 mo. RR: <10%

IP = Investigational Product
Practicalities for General Trial Design in Pancreatic Cancer

• Rationale for IP plus chemotherapy combinations.
• Chemotherapy and overlapping toxicities.
• Patients often with multiple symptoms and complications from the disease.
• 1st line molecularly-selected trials need rapid turn-around for assay results.
• Maintenance trials are of growing interest.
• Rapid movement of effective drugs to earlier treatment settings.
• KRAS inhibitors should have large role to play!
• Get research tissue.
Histologic transformation and changes to the TME as mechanisms of resistance

**Adeno-Squamous Transition (AST):** Transition to squamous cell carcinoma upon adagrasib resistance observed in 2 of 9 (22%) NSCLC cases with paired pre-/post-treatment tissue biopsies.

Awad, ..., Aguirre et al. NEJM 2022

**Epithelial-mesenchymal transition (EMT)**

Pre-Rx | Resistant
---|---
H&E | Vimentin | E-cadherin

NCSLC: Rapid autopsy s/p sotorasib
Tsai, ..., Pecot et al. JCI 2022
Histologic transformation and changes to the TME as mechanisms of resistance

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Awad,...., Aguirre et al. NEJM 2022

**Epithelial-mesenchymal transition (EMT)**

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<th>H&amp;E</th>
<th>Vimentin</th>
<th>E-cadherin</th>
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<tr>
<td>Pre-Rx</td>
<td></td>
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<tr>
<td>Resistant</td>
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NCSLC: Rapid autopsy s/p sotorasib

Tsai,...., Pecot et al. JCI 2022

**Williams et al. Cancer Res 2023**
**Raghavan et al. Cell 2021**

**Dias Costa et al. Clin Cancer Res 2022**
Translational platform for clinical trials of KRAS inhibition

Advanced Pancreatic Cancer

Serial blood and tissue biopsies

DNA, RNA Seq

Single-cell/nuc multi-omics

Histopathology & Spatial Profiling

Organoids & PDX

Rapid Biomarker Assays

Serial ctDNA and blood biomarkers

First-line Chemotherapy → Progression → KRAS Inhibitor → Progression

Diagnostic

Pre-treatment

On-treatment

Post-progression

Data analysis

Biomarkers of response and resistance

Preclinical validation

Next generation trials

Expanded analysis

Serial QOL Assessment

Diagnostic Pre-treatment On-treatment Post-progression

Data analysis Biomarkers of response and resistance Preclinical validation Next generation trials

Iterative Process
Summary

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in KRAS

• RMC-6236 is a tri-complex, KRAS\textsuperscript{MULTI(ON)} inhibitor with strong preclinical data in multiple KRAS-mutant malignancies across different KRAS variants

• Trial enrollment is ongoing at 10 U.S. sites

• Toxicity profile thus far has consisted primarily of rash, nausea/vomiting, and diarrhea.

• Early efficacy signals have been seen, with partial responses by RECISTv1.1 in patients with KRAS-mutant NSCLC and PDAC

• Additional data to be presented next month at AACR-NCI-EORTC Conference (Boston) and ESMO Congress (Madrid).
Thank you.

RMC-6236-001: Phase 1/1b Multicenter Open-Label Study of RMC-6236 in Subjects with Advanced Solid Tumors Harboring Specific Mutations in KRAS

Enrolling patients and their families
Investigators and staff at the 10 enrolling centers
Revolution Medicines study team