Revolution Medicines Announces Publications on the Discovery and Preclinical Profile of Representative of a New Class of RAS(ON) Multi-Selective Inhibitors Designed to Block Full Spectrum of Oncogenic RAS(ON) Proteins

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Two original papers in Nature *highlight the discovery and translational implications of RMC-7977, a RAS(ON) multi-selective tri-complex inhibitor that exhibits unprecedented anti-tumor activity in preclinical models of RAS-mutant pancreatic ductal adenocarcinoma (PDAC)*

First paper demonstrates RMC-7977 successfully targets signaling by both mutant and wild-type forms of RAS to drive potent and durable inhibition of RAS-mutated cancers

Second paper highlights translation-focused research with RMC-7977, which drives deep and durable anti-tumor activity, at well-tolerated doses, across a wide range of RAS-mutated PDAC preclinical models

REDWOOD CITY, Calif., April 08, 2024 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for patients with RAS-addicted cancers, today announced the publication of two peer-reviewed research papers in *Nature*. The first paper highlights the discovery and preclinical characterization of RMC-7977, a preclinical tool compound representative of a class of oral RAS(ON) multi-selective inhibitors, including the investigational drug candidate RMC-6236, that target multiple RAS variants. The second paper highlights the systematic evaluation of RMC-7977 in a wide range of preclinical models of PDAC. This original research was led by scientists at Revolution Medicines and conducted in collaboration with researchers from across the U.S. and Europe.

Oncogenic RAS proteins drive up to 30 percent of all human cancers, most notably non-small cell lung cancer (NSCLC), PDAC and colorectal cancer (CRC). RAS G12 mutations, such as G12D, G12V and G12C, predominate in human cancers. Approved KRAS-targeted cancer therapies target only one particular RAS mutation, KRAS G12C.

The first *Nature* paper describes RMC-7977, a RAS(ON) multi-selective inhibitor preclinical tool compound, which was designed to inhibit the full spectrum of oncogenic RAS mutations, including RAS codon 12 mutations (RAS G12X) as well as non-mutated wild-type RAS. RMC-7977 engages the intracellular chaperone cyclophilin A (CYPA) to form a binary complex that binds reversibly and with high affinity to RAS proteins that are in the active, GTP-bound or ON state. In preclinical studies, RMC-7977 demonstrated robust, durable anti-tumor activity at well-tolerated doses across a range of RAS-mutated NSCLC, PDAC and CRC models. Importantly, the preclinical study demonstrated that RAS(ON) multi-selective inhibitors, as represented by RMC-7977, have the potential to overcome some of the resistance mechanisms that have been shown to limit the clinical efficacy and durability of current KRAS(OFF) G12C-selective inhibitors, including adaptive signaling mechanisms mediated by activation of wild-type RAS.

The second report describes research into the pharmacology and anti-tumor activity of the tool compound, RMC-7977, which was evaluated across a diverse range of preclinical PDAC models. Broad and pronounced anti-tumor activity was observed across various preclinical models following direct RAS inhibition by RMC-7977 at exposures that were well tolerated in vivo, providing a strong preclinical rationale for evaluating broad-spectrum RAS inhibition in the clinical PDAC setting. Furthermore, careful analysis of recognized clinical resistance mechanisms in a sophisticated model of PDAC treated with RMC-7977 revealed a promising combination treatment regimen that may be capable of countering monotherapy drug resistance.

“This innovative research extends the impact of our tri-complex inhibitor platform to a wide range of common, oncogenic RAS mutants for which no targeted drugs are available, and supported the discovery of RMC-6236, our clinical-stage RAS(ON) multi-selective inhibitor. The findings reverse long-standing scientific dogma by showing that it is possible to obtain meaningful anti-tumor activity by broadly targeting the RAS class of proteins without unacceptable effects in normal tissues,” said Mark A. Goldsmith, M.D., Ph.D., chief executive officer and chairman of Revolution Medicines. “The preclinical findings reported in these scientific papers, combined with initial data we have disclosed from an ongoing clinical study of RMC-6236, support further evaluation of RMC-6236 in patients living with RAS-addicted cancers, for whom there remain large unmet medical needs.”

The investigational oral drug candidate RMC-6236 is a RAS(ON) multi-selective inhibitor designed to treat patients with cancers driven by a wide range of common RAS mutations. Revolution Medicines is currently evaluating RMC-6236 as monotherapy in a first-in-human trial in patients with advanced solid tumors harboring G12X, G13X, and Q61X mutations (NCT05379985). Based on promising preliminary data in this trial, planning is underway to initiate pivotal studies of RMC-6236 as monotherapy in NSCLC and PDAC. RMC-6236 is also being evaluated in combination with pembrolizumab with or without chemotherapy in patients with advanced RAS-mutated solid tumors (NCT06162221) and in combination with RMC-6291, the company’s investigational RAS(ON) G12C-selective inhibitor, for patients with advanced KRAS G12C-mutated solid tumors (NCT06128551).

The scientific papers published in *Nature* can be accessed at the following links:

- “Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy”
- “Tumor-selective effects of active RAS inhibition in pancreatic ductal adenocarcinoma”

About Revolution Medicines, Inc.
Revolution Medicines is a clinical-stage oncology company developing novel targeted therapies for RAS-addicted cancers. The company’s R&D pipeline comprises RAS(ON) inhibitors designed to suppress diverse oncogenic variants of RAS proteins, and RAS companion inhibitors for use in combination treatment strategies. The company’s RAS(ON) inhibitors RMC-6236, a RAS(ON) multi-selective inhibitor, RMC-6291, a RAS(ON) G12C-selective inhibitor, and RMC-9805, a RAS(ON) G12D-selective inhibitor, are currently in clinical development. Additional RAS(ON) mutant-selective inhibitors in the company’s development pipeline include RMC-5127 (G12V), RMC-0708 (Q61H) and RMC-8839 (G13C).

Forward Looking Statements
This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. Any statements in this press release that are not historical facts may be considered "forward-looking statements," including without limitation statements

regarding the potential advantages of Revolution Medicines' preclinical and clinical candidates, including the potential efficacy, durability, tolerability, and combination potential of RMC-7977 and RMC-6236 and their ability to overcome resistance mechanisms; the company's development plans and its ability to advance its portfolio and R&D pipeline, including the company's potential evaluation of broad-spectrum RAS inhibition in the clinical PDAC setting and its planned initiation of pivotal studies of RMC-6236 as monotherapy in NSCLC and PDAC; the outcome of the company's preclinical studies and clinical trials; the potential application of the company's tri-complex inhibitor platform to a wide range of oncogenic RAS mutations; and the company's expectations regarding the size of the unmet medical needs its product candidates could address, if approved for commercial use. Forward-looking statements are typically, but not always, identified by the use of words such as "may," "will," "would," "believe," "intend," "plan," "anticipate," "estimate," "expect," and other similar terminology indicating future results. Such forward-looking statements are subject to substantial risks and uncertainties that could cause the company's development programs, future results, performance or achievements to differ materially from those anticipated in the forward-looking statements. Such risks and uncertainties include without limitation risks and uncertainties inherent in the drug development process, including the company's programs' early stage of development, the process of designing and conducting preclinical studies and clinical trials, risks that the results of prior preclinical models or studies may not be predictive of future clinical trials, clinical efficacy or other future results, the regulatory approval processes, the timing of regulatory filings, the challenges associated with manufacturing drug products, the company's ability to successfully establish, protect and defend its intellectual property, other matters that could affect the sufficiency of the company's capital resources to fund operations, reliance on third parties for manufacturing and development efforts, changes in the competitive landscape, the risk that the wind-down of EQRx, Inc. could take longer than anticipated or result in unexpected costs, and the effects on the company's business of global events, such as international conflicts or pandemics. For a further description of the risks and uncertainties that could cause actual results to differ from those anticipated in the forward-looking statements, as well as risks relating to the business of Revolution Medicines in general, see Revolution Medicines' Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 26, 2024, and its future periodic reports to be filed with the Securities and Exchange Commission. Except as required by law, Revolution Medicines undertakes no obligation to update any forward-looking statements to reflect new information, events, or circumstances, or to reflect the occurrence of unanticipated events.

Revolution Medicines Media & Investor Contact: Erin Graves 650-779-0136 egraves@revmed.com