Revolution Medicines Announces Publication on the Discovery of and Translational Research for RMC-6236, an Investigational RAS(ON) Multi-Selective Tri-Complex Inhibitor Designed to Block Full Spectrum of Oncogenic RAS(ON) Proteins

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Simultaneous publication and presentation of RMC-6236 chemical structure, preclinical data and case studies during the "KRAS: Broadening the Attack Beyond G12C with Small Molecules and Immuno-Oncology" Session at AACR 2024 in San Diego

REDWOOD CITY, Calif., April 09, 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 a peer-reviewed research paper in *Cancer Discovery.* The scientific paper details the discovery and preclinical to clinical translation for RMC-6236, an investigational RAS(ON) multi-selective inhibitor, and includes exemplary case studies from the current Phase 1/1b clinical trial demonstrating the initial anti-tumor activity of RMC-6236. 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), colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC). RAS G12 mutations, such as G12D, G12V and G12C, predominate in human cancers. Currently approved KRAS-targeted cancer therapies target one particular KRAS mutation, KRAS G12C, in the GDP-bound (OFF) state. The paper describes the discovery of RMC-6236, an oral, multi-selective inhibitor of the active GTP-bound (ON) state of both mutant and wild-type RAS. In preclinical studies, RMC-6236 was effective in inhibiting the growth of RAS-dependent tumor cells, while sparing normal tissues. RMC-6236 was found to be well-tolerated and drove deep and durable tumor regressions across multiple cancer types including NSCLC, PDAC, CRC, gastric and gynecologic cancers, with tumor models dependent on KRAS G12 mutations being particularly sensitive. This benefit was found to extend to models with K/N/HRAS hotspot mutations at G13 and Q61 as well.

The paper also highlights translational pharmacokinetics (PK)/efficacy and PK/pharmacodynamics modeling, which predicted that daily doses of 100 mg and 300 mg would achieve tumor control and objective responses, respectively, in patients with RAS-driven tumors. Consistent with this, case studies from the Phase 1/1b RMC-6236 monotherapy clinical trial are featured, describing two patients with advanced KRAS-G12V NSCLC and KRAS-G12D PDAC, respectively, who were treated with 300 mg of RMC-6236 daily. Each of these two patients achieved a complete response as best response demonstrating the potential anti-tumor activity of RMC-6236.

"The discovery of RMC-6236 allowed for the first-ever therapeutic evaluation of targeted concurrent inhibition of both canonical mutant and wild-type RAS-GTP (RAS(ON)) in RAS-driven cancers. The RMC-6236 clinical data that we have shared not only provide platform validation of our tri-complex inhibitor approach, but also refute the dogma that one could not induce anti-tumor activity by broad inhibition of multiple RAS variants, including wild-type RAS, at doses that would be well tolerated," said Steve Kelsey, M.D., president, research and development of Revolution Medicines. "The research summarized in our *Cancer Discovery* paper, combined with the preliminary RMC-6236 clinical data presented in late 2023, provide us and our investigators with the confidence to advance and expand our RMC-6236 clinical development program."

Revolution Medicines is currently evaluating RMC-6236 as monotherapy in a Phase 1/1b trial in patients with advanced solid tumors harboring G12X, G13X and Q61X mutations (NCT05379985). Following promising preliminary data in this Phase 1/1b study, 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).

Today's publication coincides with the company's presentation of RMC-6236 preclinical data and additional clinical case studies during the "KRAS: Broadening the Attack Beyond G12C with Small Molecules and Immuno-Oncology" session today at the American Association for Cancer Research (AACR) Annual Meeting 2024 in San Diego.

The scientific paper can be accessed at the following link: https://doi.org/10.1158/2159-8290.CD-24-0027.

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 preclinical candidates, including the potential efficacy, durability, tolerability and combination potential of RMC-6236; validation of the company's tri-complex platform; and the company's RMC-6236 and RMC-6291 development plans. 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.

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