



Revolution Medicines Announces Publication Describing Molecular Basis of Tri-Complex Inhibitors Targeting Oncogenic RAS(ON) Proteins

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Science Report on KRAS^{G12C}(ON)-Selective Inhibitors Provides Preclinical Proof-of-Principle for Company's RAS Innovation Engine and Broad Pipeline

REDWOOD CITY, Calif., Aug. 17, 2023 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for RAS-addicted cancers, today announced the publication of a peer-reviewed research paper in *Science*. This original research was led by scientists at Revolution Medicines and conducted in collaboration with researchers from Memorial Sloan Kettering Cancer Center.

The paper describes the Revolution Medicines tri-complex inhibitor approach to developing novel small molecules with high affinity and selectivity for the active state of mutant RAS, or RAS(ON), proteins that are common causes of human cancer and were previously considered undruggable. Specifically, it describes the creation of innovative, natural product-inspired, orally bioavailable small molecules, including the tool compound RMC-4998 and the clinical candidate RMC-6291. These compounds are shown to remodel the surface of the cellular chaperone cyclophilin A (CYPA) to create a neomorphic interface with affinity for active KRAS and achieve high selectivity for mutant KRAS^{G12C} via covalent, irreversible binding to the cysteine residue in the active state of this variant RAS protein that often drives formation of lung and colorectal cancers. KRAS^{G12C}(ON) trapped in these tri-complexes is sterically blocked from interacting with downstream effectors that transmit cancer-causing signals. Both RMC-4998 and RMC-6291 inactivate oncogenic signaling in KRAS^{G12C}-dependent tumor cells and drive deep and durable tumor regressions in human xenograft models of these cancers.

"This research serves as preclinical validation of our tri-complex RAS(ON) inhibitor platform and confirms our ability to design potent, selective small molecules that target KRAS mutations in their active or ON state," said Steve Kelsey, M.D., president, research and development at Revolution Medicines. "These data provide the rationale for the RMC-6291 clinical program, our first mutant-selective RAS(ON) inhibitor to enter clinical development, which is currently underway. We look forward to sharing a preliminary report of the clinical profile for RMC-6291 at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (Triple Meeting) in October 2023."

The investigational agent RMC-6291, an oral, selective, covalent inhibitor of KRAS^{G12C}(ON) designed to treat patients with cancers driven by the KRAS^{G12C} variant, is the first of the company's mutant-selective RAS(ON) inhibitors to enter clinical development and the first reported clinical-stage inhibitor of KRAS^{G12C} that uses this highly differentiated mechanism of action. Revolution Medicines is currently evaluating RMC-6291 as monotherapy in a Phase 1/1b trial in patients with advanced KRAS^{G12C} mutant solid tumors ([NCT05462717](https://clinicaltrials.gov/ct2/show/study/NCT05462717)).

The manuscript published in *Science* is entitled, "Chemical remodeling of a cellular chaperone to target the active state of mutant KRAS" and can be accessed at <https://www.science.org/doi/10.1126/science.adg9652>.

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 (RAS^{MULTI}), RMC-6291(KRAS^{G12C}) and RMC-9805 (KRAS^{G12D}) are currently in clinical development. Additional RAS(ON) Inhibitors in the company's pipeline include RMC-0708 (KRAS^{Q61H}) which is currently in IND-enabling development, RMC-8839 (KRAS^{G13C}), and additional compounds targeting other RAS variants. RAS Companion Inhibitors in clinical development include RMC-4630 (SHP2) and RMC-5552 (mTORC1/4EBP1).

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 tolerability and potential efficacy of Revolution Medicines' clinical candidates, including RMC-6291 and its clinical profile; the outcome of the company's clinical trials, including the Phase 1/1b study of RMC-6291; and validation of the company's platform and its ability to design small molecules. 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 our 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 and clinical trials, 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 and the effects on our business of the worldwide COVID-19 pandemic. For a further description of the risks and uncertainties that could cause actual results to differ from those anticipated in these forward-looking statements, as well as risks relating to the business of Revolution Medicines in general, see Revolution Medicines' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 8, 2023, 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.