Revolution Medicines Announces Publication of a Peer-Reviewed Research Paper in Science on the Discovery and Development of Zoldonrasib, a RAS(ON) G12D-Selective Inhibitor

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REDWOOD CITY, Calif., July 24, 2025 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a late-stage clinical oncology company developing targeted therapies for patients with RAS-addicted cancers, today announced the publication of a peer-reviewed research paper in *Science*. The scientific paper details the discovery and development of zoldonrasib (RMC-9805), a RAS(ON) G12D-selective covalent inhibitor.

Oncogenic RAS mutations are observed in approximately 92% of pancreatic ductal adenocarcinoma (PDAC), 50% of colorectal cancer, and 30% of non-small cell lung cancer (NSCLC) cases. RAS G12D, an oncogenic variant of RAS that contains an aspartic acid in place of glycine at amino acid 12, is one of the most common RAS mutations in human solid tumors. Historically, it has been particularly challenging to target aspartic acid residues with covalent inhibitors. This publication details the novel mechanism of zoldonrasib, a member of the differentiated class of targeted protein binders called tri-complex inhibitors. This natural product-like compound successfully overcomes the challenge of engaging aspartic acid residues by leveraging a neomorphic protein-protein interface between the cellular chaperone cyclophilin A and activated RAS, or RAS(ON), to selectively catalyze covalent bond formation with RAS(ON) G12D proteins. Data reported in this paper demonstrate that this activity drives deep and durable tumor regressions in preclinical models of multiple tumor types with KRAS G12D mutations.

“The tri-complex inhibitor modality has proven to be a productive approach to solving the challenge of developing mutant-selective inhibitors for RAS variants beyond the G12C substitution, as demonstrated by zoldonrasib that targets the G12D variant,” said Jan Smith, Ph.D., chief scientific officer of Revolution Medicines. “This report demonstrates the novel features of zoldonrasib that enable it to bind to the active or RAS(ON) state, including a highly novel covalent bond formed selectively with the substituted aspartic acid in this oncogenic variant. The preclinical profile combined with recent clinical data presentations provide an encouraging picture of the therapeutic potential for zoldonrasib in cancers caused by RAS G12D and further validate the broad utility of this drug discovery approach.”

The full manuscript, titled “A neomorphic protein interface catalyzes covalent inhibition of RAS G12D aspartic acid in tumors,” is available online at *Science*.

Zoldonrasib is currently undergoing evaluation in several clinical trials, including RMC-9805-001 (NCT06040541), a multicenter, open-label, dose escalation and dose-expansion Phase 1 study designed to evaluate zoldonrasib in patients with advanced solid tumors harboring a KRAS G12D mutation. NSCLC results from this study were presented in April 2025 at the American Academy for Cancer Research annual meeting and PDAC results from this study were presented in October 2024 at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics.

About Revolution Medicines, Inc.
Revolution Medicines is a late-stage clinical oncology company developing novel targeted therapies for patients with RAS-addicted cancers. The company’s R&D pipeline comprises RAS(ON) inhibitors designed to suppress diverse oncogenic variants of RAS proteins. The company’s RAS(ON) inhibitors daraxonrasib (RMC-6236), a RAS(ON) multi-selective inhibitor; elironrasib (RMC-6291), a RAS(ON) G12C-selective inhibitor; and zoldonrasib (RMC-9805), a RAS(ON) G12D-selective inhibitor, are currently in clinical development. The company anticipates that RMC-5127, a RAS(ON) G12V-selective inhibitor, will be its next RAS(ON) inhibitor to enter clinical development. Additional development opportunities in the company’s pipeline focus on RAS(ON) mutant-selective inhibitors, including RMC-0708 (Q61H) and RMC-8839 (G13C). For more information, please visit www.revmed.com and follow us on LinkedIn.

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 progression of clinical studies and findings from these studies, including the safety, tolerability and antitumor activity of the company’s candidates being studied and the durability of these results; dosing and enrollment in the company’s clinical trials; and the potential of zoldonrasib as a therapeutic option for pancreatic ductal adenocarcinoma or non small cell lung cancer. 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’ current stage of development, the process of designing and conducting preclinical and clinical trials, risks that the results of prior clinical trials 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, and the effects on the company’s business of the global events, such as international conflicts or global pandemics. 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’ Annual Report on Form 10-K filed with the Securities and Exchange Commission (the “SEC”) on May 7, 2025, and its future periodic reports to be filed with the SEC. 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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