Revolution Medicines Announces Publication Describing Design and Synthesis of RMC-5552, a First-in-Class, Bi-Steric mTORC1-Selective Inhibitor

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Findings Published in the Journal of Medicinal Chemistry Demonstrate Compound's Exceptional Selectivity for mTORC1 over mTORC2

Tumor Regressions Observed During Combination Treatment with a Bi-Steric mTORC1-Selective Inhibitor and a KRAS^{G12C}-Selective Inhibitor in Preclinical Lung Cancer Model that is Resistant to KRAS^{G12C} Inhibitor Monotherapy

REDWOOD CITY, Calif., Dec. 19, 2022 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for RAS-addicted cancers, today announced publication of a manuscript in the *Journal of Medicinal Chemistry* that details the discovery efforts leading to RMC-5552, the company's first-in-class, bi-steric mTORC1-selective inhibitor. The manuscript describes the unprecedented compound profile that includes 40-fold selectivity for mTORC1 over mTORC2 and greater than 53-fold selectivity over other lipid kinases. The paper also shows that selective mTORC1 inhibition using the company's related preclinical tool compound (RMC-6272) in combination with a covalent KRAS^{G12C} inhibitor induced tumor regressions in a preclinical model of KRAS^{G12C} mutant non-small cell lung cancer (NSCLC) that exhibits resistance to KRAS^{G12C} inhibitor monotherapy.

RMC-5552 is designed to suppress phosphorylation and inactivation of 4EBP1, a key translational regulator of oncogene expression, in cancers with hyperactive mTORC1 signaling. This bi-steric compound is designed to bind simultaneously to two different sites on mTORC1 to drive deep inhibition of mTORC1 while maintaining selectivity for mTORC1 over mTORC2, a unique profile compared to prior generations of mTOR inhibitors. Revolution Medicines is currently evaluating RMC-5552 as monotherapy in a Phase 1/1b clinical trial in patients with refractory solid tumors (NCT04774952), and initial antitumor activity has been reported. The company plans to evaluate RMC-5552 in combination with RAS(ON) inhibitors in patients with cancers harboring mutations in both RAS and the mTOR pathways.

"The *Journal of Medicinal Chemistry* manuscript details the sophisticated structure-based chemical design and synthesis employed by our drug discovery team that produced RMC-5552," said Steve Kelsey, M.D., president, research and development at Revolution Medicines. "The differentiated antitumor and tolerability profile of RMC-5552 in the preclinical setting compared to earlier mTORC inhibitors provides a strong rationale for evaluating it in patients with tumors that have abnormally high mTORC1 growth signaling, including in combination with our RAS(ON) Inhibitors in patients with tumors that have both RAS and mTORC1 pathway co-mutations."

The manuscript published in the *Journal of Medicinal Chemistry* is titled, "Discovery of RMC-5552, a Selective Bi-Steric Inhibitor of mTORC1, for the Treatment of mTORC1-activated Tumors," and can be accessed at: https://doi.org/10.1021/acs.jmedchem.2c01658

About mTORC1

The mTOR Complex 1 (mTORC1) is a central node within the mTOR signaling pathway and a critical regulator of metabolism, growth, and proliferation in cancer cells. Oncogenic mutations of genes encoding proteins that lie upstream of mTOR, including PI3K, PTEN, and STK11, can drive abnormal activation of mTORC1 and subsequent inactivation of the tumor suppressor 4EBP1. Selective inhibition of mTORC1 to reactivate 4EBP1 is a potential therapeutic strategy for patients with tumors bearing such mutations. These mutations are often co-occurring with RAS mutations in RAS-addicted tumors and combinations of mTORC1- and RAS-targeted inhibitors may be of particular benefit in this context.

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}) and RMC-6291(KRAS^{G12C}) are currently in clinical development. Additional RAS(ON) Inhibitors in the company's pipeline include RMC-9805 (KRAS ^{G12D}), 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-5552; the outcome of the company's clinical trials, including the Phase 1/1b study of RMC-5552; and the company's plans to combine RMC-5552 with RAS inhibitors and the potential benefits of any such combination. 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 November 7, 2022, 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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