Revolution Medicines Announces Publication of Scientific Paper Describing Novel Class of Anti-Tumor Compounds Targeting mTORC1

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Findings Published in Nature Chemical Biology Support Clinical Development of RMC-5552, the Company's First-in-Class, Phase 1/1b Bi-steric mTORC1-Selective Inhibitor

REDWOOD CITY, Calif., June 24, 2021 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage precision oncology company focused on developing targeted therapies to inhibit frontier targets in RAS-addicted cancers, today announced the publication of an original scientific paper in *Nature Chemical Biology* describing anti-tumor effects of bi-steric mTORC1-selective inhibitors that potently suppress phosphorylation of 4EBP1, a key translational regulator of oncogene expression. In preclinical models of cancers with mutations that drive mTORC1 hyperactivation, a series of bi-steric inhibitors demonstrated the favorable anti-tumor effects and tolerability of deeply and selectively inhibiting mTORC1 compared to earlier generations of mTOR inhibitors. Mutations that cause hyperactive mTORC1 signaling are found in tumors with and without co-existent RAS mutations. This original research was led by scientists at Revolution Medicines and conducted in collaboration with the Neal Rosen Lab at the Memorial Sloan Kettering Cancer Center, as well as researchers from McGill University and The Karolinska Institute.

Revolution Medicines recently advanced RMC-5552, the company's investigational first-in-class bi-steric mTORC1 inhibitor, into clinical development. RMC-5552 is a potent and selective inhibitor of mTORC1 that is being developed as an anti-cancer therapeutic for patients with solid tumors that exhibit hyperactivation of the mTOR pathway, including certain RAS-addicted cancers. The compound is designed to inhibit mTORC1 and thereby protect the natural tumor suppressor activity of 4EBP1, without the undesirable inhibition of mTORC2. RMC-5552 has demonstrated anti-tumor activity in a wide variety of preclinical models. Revolution Medicines has also reported *in vivo* data demonstrating that RMC-5552 may increase anti-tumor activity in combination with $KRAS^{G12C}$ inhibitors in lung and colon cancers harboring both KRAS mutations and co-mutations in the mTOR signaling pathway that can cause resistance to single agent RAS inhibition.

"The paper published in *Nature Chemical Biology* highlights the therapeutic promise of mTORC1-selective bi-steric inhibitors in the treatment of tumors driven by the genomic activation of the mTORC1 pathway. Specifically, the published research details the manner in which these selective inhibitors of mTORC1 potently inhibit tumor growth while causing less toxicity and receptor reactivation, a potential mechanism of adaptive resistance, as compared to conventional mTOR inhibitors," said Steve Kelsey, M.D., president, research and development at Revolution Medicines. "These study results offer compelling rationale for our recently initiated clinical development program for RMC-5552."

The company recently initiated a multicenter, open-label dose-escalation and dose-expansion Phase 1/1b clinical trial designed to evaluate the safety, tolerability, preliminary efficacy and pharmacokinetics of RMC-5552 in patients with advanced relapsed/refractory solid tumors. Results from this study will inform identification of the maximum tolerated dose (MTD) and selection of recommended Phase 2 dose and schedule (RP2DS) for further evaluation of the compound.

The paper published in *Nature Chemical Biology* is titled, "Selective inhibitors of mTORC1 activate 4EBP1 and suppress tumor growth," and can be accessed at: https://www.nature.com/articles/s41589-021-00813-7

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 precision oncology company focused on developing novel targeted therapies to inhibit high-value frontier targets in RAS-addicted cancers. The company possesses sophisticated structure-based drug discovery capabilities built upon deep chemical biology and cancer pharmacology know-how and innovative, proprietary technologies that enable the creation of small molecules tailored to unconventional binding sites.

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. RAS(ON) Inhibitors in development include RMC-6291 and RMC-6236, and a pipeline of research compounds targeting additional RAS variants. RAS Companion Inhibitors in development include RMC-4630, RMC-5552, and RMC-5845.

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; identification of the MTD and selection of a RP2DS for RMC-5552; the strategy of developing drug combinations that can achieve maximum clinical benefit; and the potential increase in anti-tumor activity when combining RMC-5552 with other agents, including $KRAS^{G12C}$ inhibitors. 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 May 10, 2021, 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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