REVOLUTION Medicines Announces Dosing of First Patient in RMC-4630-02, a Phase 1b/2 Trial Combining RMC-4630 with a MEK Inhibitor

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Combination Inhibits Upstream and Downstream Targets in Oncogenic RAS Signaling Pathway, Offering Potential for Synergistic Anti-Tumor Benefit

REDWOOD CITY, Calif., Sept. 17, 2019 /PRNewswire/ -- REVOLUTION Medicines, Inc., a clinical-stage oncology company focused on developing novel targeted therapies to inhibit elusive frontier targets within notorious cancer pathways, today announced dosing of the first patient in an open-label, Phase 1b/2 dose-escalation and dose-expansion study of RMC-4630 in combination with cobimetinib (Cotellic®) in patients with relapsed/refractory solid tumors harboring specific genomic mutations. RMC-4630, a SHP2 inhibitor, and Cotellic®, a MEK inhibitor, are selective inhibitors of oncogenic targets at distinct positions within the RAS signaling cascade that is frequently exploited by human cancers and may develop adaptive resistance to single agent treatment. A combination of these complementary mechanisms of action demonstrated synergistic anti-tumor effects in preclinical cancer models carrying select oncogenic mutations of RAS or associated proteins. These findings provide a compelling scientific rationale to explore the potential of this combination regimen in patients with tumors driven by such mutations.

RMC-4630 is a potent and orally bioavailable small molecule that selectively inhibits the activity of SHP2, an upstream cellular protein that plays a key role in modulating cell growth by transmitting signals from receptor tyrosine kinases to RAS. RMC-4630 and SHP2 are the focus of an exclusive global research, development and commercialization agreement with Sanofi. Cobimetinib, marketed in the U.S. by Genentech, a member of the Roche group, selectively inhibits the activity of MEK, a downstream effector of RAS that affects cell survival and growth. Under a clinical collaboration agreement, Genentech is providing cobimetinib for the combination study being conducted by REVOLUTION Medicines.

"Preclinical and clinical research have clearly established that oncogenic signaling involving RAS can exploit multiple cellular mechanisms to overcome therapeutic inhibition of individual pathway targets. We believe that rationally designed drug combinations inhibiting multiple nodes within the pathway may provide an effective strategy for defeating these inherent resistance mechanisms," said Mark A. Goldsmith, M.D., Ph.D., president and chief executive officer of REVOLUTION Medicines. "While we continue studying RMC-4630 as a single agent in our first clinical study, RMC-4630-01, we are also evaluating its effects in combination with a MEK inhibitor in this second study, RMC-4630-02."

The Phase 1b/2 RMC-4630-02 study will evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of RMC-4630 and cobimetinib in adult patients with relapsed/refractory solid tumors that harbor specific genomic mutations. The trial will seek to identify the maximum tolerated dose of RMC-4630 in combination with cobimetinib as well as the recommended dose for a subsequent Phase 2 trial of the combination.

Cobimetinib is approved in the U.S. for the treatment of patients with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive unresectable or metastatic melanoma in combination with vemurafenib (Zelboraf®).

About RMC-4630 and Sanofi Collaboration

RMC-4630 is currently being evaluated in a Phase 1 monotherapy clinical trial (RMC-4630-01) for a range of tumor types featuring specific, molecularly-defined oncogenic mutations, as well as a Phase 1b/2 study (RMC-4630-02) in combination with cobimetinib in patients with relapsed/refractory solid tumors displaying specific genomic mutations. The RMC-4630 program is the focus of an exclusive global research, development and commercialization agreement with Sanofi, under which REVOLUTION Medicines received a $50 million upfront payment, and Sanofi will cover research and development costs for the joint SHP2 program. Sanofi received an exclusive worldwide license for global commercialization of any approved products targeting SHP2, subject to a U.S. co-promote right for REVOLUTION Medicines. The companies will enter into a 50/50 profit and loss share arrangement in the U.S., and REVOLUTION Medicines will receive a tiered royalty reaching mid-double digits on sales in other markets. REVOLUTION Medicines could also receive more than $500 million in development and regulatory milestone payments.

About REVOLUTION Medicines, Inc.

REVOLUTION Medicines is a clinical-stage oncology company focused on developing novel targeted therapies to inhibit elusive high-value frontier cancer targets within notorious growth and survival pathways, with particular emphasis on RAS and mTOR signaling pathways, to outsmart cancer. The company possesses sophisticated oncology drug discovery capabilities built upon deep scientific knowledge of the biology of cancer pathways and innovative, proprietary technologies that enable the creation of small molecules that target atypical drug binding sites.

The company's pipeline includes RMC-4630, a clinical-stage drug candidate that selectively inhibits the activity of SHP2. Additionally, the company is developing a broad portfolio of inhibitors of other key frontier oncology targets within the notorious RAS pathway, as well as the related mTOR signaling cascade. These include inhibitors of multiple mutant RAS proteins and SOS1, as well as RMC-5552, a development candidate within our 4EBP1/mTORC1 program that is advancing into IND-enabling studies.

For more information, please visit: www.revmed.com

Cotellic® is the registered trademark of Genentech, Inc. (a member of the Roche Group).

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