Revolution Medicines Reports Progress and Expansion of Combination Strategy with RMC-4630 as Therapeutic Backbone for RAS-Addicted Cancers

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Plenary Presentation at EORTC-NCI-AACR 32nd Symposium on Molecular Targets and Cancer Therapeutics Describes Encouraging Tolerability and Exposure Profiles for RMC-4630 Combined with Cobimetinib and Early Evidence of Clinical Activity in RAS^{mut} Colorectal Cancers

Company Also Announces New Clinical Collaboration with AstraZeneca to Study RMC-4630 in Combination with an Emerging AstraZeneca Asset Targeting KRAS^{G12C}

REDWOOD CITY, Calif., Oct. 24, 2020 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage precision oncology company developing targeted therapies to inhibit frontier targets in RAS-addicted cancers, today reported interim data from the company's ongoing Phase 1b/2 clinical trial (RMC-4630-02) evaluating the combination of RMC-4630 and cobimetinib (Cotellic®) in an oral presentation by Johanna C. Bendell, M.D., Sarah Cannon Research Institute, Nashville, TN in a plenary session at the EORTC-NCI-AACR 32nd Symposium on Molecular Targets and Cancer Therapeutics (ENA 2020). Interim results suggest that a dual intermittent dosing strategy for RMC-4630 and cobimetinib exceeds target plasma exposures for each drug based on preclinical models of RAS pathway-driven cancers that project potential clinical activity. The adverse event profile of the combination, which was consistent with expected on-pathway effects of both drugs, was tolerable under the dual intermittent dosing schedule.

The ongoing Phase 1b/2 RMC-4630-02 trial includes an open-label, dose-escalation and dose-expansion study arm designed to 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 RAS pathway mutations. The results of this study will inform Revolution Medicines' pending selection of a recommended Phase 2 dose and schedule for the drug combination to be evaluated further in one or more expansion cohorts of patients selected by tumor genotype and histotype that are expected to initiate in 2020.

While evaluation of efficacy outcomes is not a primary objective of the dose escalation portion of the RMC-4630-02 study, investigators reported preliminary evidence of anti-tumor activity in patients with colorectal cancer driven by KRAS mutations. As of the data cut-off date, tumor volume reduction was observed in three of seven patients with colorectal cancers harboring KRAS mutations who were treated at the highest dose of RMC-4630, including one unconfirmed partial response in a patient carrying a KRAS^{G12D} mutation.

Expansion of Combination Program

Revolution Medicines also announced that it has signed an agreement with AstraZeneca (LSE/STO/Nasdaq: AZN) to enter a clinical collaboration to study RMC-4630 in combination with an emerging asset from AstraZeneca's preclinical efforts targeting KRAS ^{G12C}. Under the agreement, AstraZeneca will sponsor and conduct this combination study and Revolution Medicines will provide clinical supply of RMC-4630.

Separately, Revolution Medicines and Amgen are collaborators in an ongoing Amgen-sponsored clinical trial studying RMC-4630 in combination with AMG 510 (sotorasib), an investigational KRAS^{G12C}(OFF) inhibitor.

"Drug combinations are likely to be critical for defeating inherent drug resistance mechanisms exploited by RAS-addicted cancers, and both the data presented at ENA 2020 and the new clinical collaboration announced today represent important steps forward in developing RMC-4630 as a backbone of such combination therapies. The ENA presentation focuses on cancers with RAS mutations lacking a mutant-selective inhibitor, and suggest that RMC-4630 and cobimetinib can be combined through an innovative dual intermittent dosing schedule to drive anti-tumor activity in advanced colorectal cancers," said Mark A. Goldsmith, M.D., Ph.D., chief executive officer and chairman of Revolution Medicines. "We are currently refining a recommended Phase 2 dose and schedule to evaluate further for safety, tolerability and anti-tumor activity in dedicated expansion patient cohort(s)."

"We are also excited to collaborate with AstraZeneca to study RMC-4630 in combination with an emerging asset from AstraZeneca's pipeline targeting KRAS^{G12C}(OFF) for tumors carrying a KRAS^{G12C} mutation, a planned study that represents an expansion of our commitment to RMC-4630 as a backbone for combinations with RAS-mutant inhibitors. We also continue growing our exciting pipeline of direct inhibitors of oncogenic RAS(ON) variants, including our direct inhibitors of KRAS^{G12C}(ON) and KRAS^{G12D}(ON) currently in lead optimization."

RMC-4630 and cobimetinib are targeted inhibitors of oncogenic proteins at distinct positions within the RAS signaling cascade that is frequently exploited by human cancers and may develop adaptive resistance to single agent treatment. RMC-4630 is a potent and orally bioavailable small molecule designed to selectively inhibit 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. Cobimetinib, marketed in the U.S. by Genentech, a member of the Roche group, inhibits the activity of MEK, a downstream effector of RAS that affects cell survival and growth. 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®). Cobimetinib is provided by Genentech for the RMC-4630-02 study under a clinical collaboration agreement with Revolution Medicines.

About RMC-4630

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, a Phase 1b/2 trial (RMC-4630-02) in combination with cobimetinib in patients with relapsed/refractory solid tumors displaying specific genomic mutations, a Phase 1b study (CodeBreaK 101) in combination with AMG 510 in patients with advanced solid tumors harboring the KRAS^{G12C} mutation, and a Phase 1 study in combination with pembrozilumab in patients with advanced malignancies.

The SHP2 inhibitor program, including RMC-4630, is the focus of an exclusive global research, development and commercialization agreement with Sanofi.

About Revolution Medicines, Inc.

Revolution Medicines is a clinical-stage precision oncology company 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 various oncogenic variants of RAS proteins, and RAS Companion Inhibitors for use in combination treatment strategies. RAS(ON) Inhibitors include compounds targeting $KRAS^{G12C}$(ON), $KRAS^{G12D}$(ON) and other RAS variants. RAS Companion Inhibitors include RMC-4630 targeting SHP2, RMC-5552 targeting mTORC1, and inhibitors of SOS1.

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

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 results of the ongoing RMC-4630-02 trial and Revolution Medicines' ability to select a recommended Phase 2 dose and schedule for this combination and to evaluate one or more expansion cohorts, statements regarding the proposed combination study with AstraZeneca, the ability of drug combinations to defeat drug resistance mechanisms exploited by RAS-addicted cancers, the utility of RMC-4630 as a backbone for combination treatments and the company's ability to develop it in this capacity , the growth of the company's pipeline of RAS(ON) inhibitors, and the potential benefits of, and markets for, Revolution Medicines' potential product candidates. 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 Revolution Medicines' 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, Revolution Medicines' ability to successfully establish, protect and defend its intellectual property, other matters that could affect the sufficiency of Revolution Medicines' capital resou rces 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 10, 2020, 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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