Revolution Medicines Presents Encouraging Clinical Data for RMC-6236 and RMC-6291 at 2023 Triple Meeting

October 13, 2023

Clinical dose escalation data for RMC-6236, a RAS^{MULTI}(ON) Inhibitor, show oral bioavailability, well-tolerated safety profile and preliminary evidence of anti-tumor activity across multiple RAS mutations

First clinical data presentation for RMC-6291, a RAS^{G12C}(ON) Inhibitor, highlights encouraging initial tolerability, safety and differentiated anti-tumor activity

Investor webcast to be held Sunday, October 22 at 12:30pm Eastern Time

REDWOOD CITY, Calif., Oct. 13, 2023 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for RAS-addicted cancers, today announced encouraging preliminary clinical data for RMC-6236, its RAS^{MULTI}(ON) Inhibitor, and RMC-6291, its RAS^{G12C}(ON) Inhibitor, from the respective Phase 1/1b studies. These data were presented during the 2023 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics ("Triple Meeting") in Boston, October 11-15, 2023.

"We are pleased to report encouraging clinical data for both RMC-6236 and RMC-6291, two pioneering RAS(ON) Inhibitors that are providing strong validation of our RAS(ON) Inhibitor platform broadly. The RMC-6236 safety data support that this highly innovative, oral RAS^{MULTI} Inhibitor is generally well tolerated across dose levels in patients, exhibits dose-dependent pharmacokinetics reaching exposures predicted preclinically to induce tumor regressions and induces molecular responses (ctDNA) and radiographic regressions suggestive of anti-tumor activity targeting multiple common RAS mutants that cause cancer, including KRAS^{G12D} and KRAS^{G12V}," said Mark A. Goldsmith, M.D., Ph.D., chief executive officer and chairman of Revolution Medicines. "The RMC-6291 data provide important initial evidence that this mutant-selective, oral RAS ^{G12C}(ON) Inhibitor can provide mechanistic and clinically meaningful differentiation from KRAS^{G12C}(OFF) inhibitors, as indicated by encouraging clinical responses in NSCLC patients previously treated with a KRAS^{G12C}(OFF) inhibitor and in KRAS^{G12C}(OFF) inhibitor naïve CRC patients at doses that are generally well tolerated."

"These data support our ongoing development of RMC-6236 and RMC-6291, both as monotherapy and in various combinations, including as a RAS(ON) Inhibitor doublet. We will continue evaluating these exciting compounds toward the goal of bringing new and effective therapies to patients living with RAS-addicted cancers, and remain committed to our rich pipeline of differentiated mutant-selective RAS(ON) Inhibitors, as there is significant need for new treatment options."

Phase 1/1b Trial of RMC-6236, RAS^{MULTI}(ON) Inhibitor
The Phase 1/1b trial is a multicenter, open-label, dose-escalation and dose-expansion study designed to evaluate RMC-6236 as monotherapy in patients with advanced solid tumors harboring KRAS^{G12X} mutations. As of the September 11, 2023 data cut-off, the most common G12 mutations in patients enrolled included G12D (51%); G12V (28%); G12R (11%); G12A (6%); and G12S (4%). Patients with KRAS^{G12C} mutations were excluded from the study due to the availability of currently approved KRAS^{G12C}(OFF) inhibitors. A total of 131 patients (69 PDAC, 47 NSCLC, 10 CRC, 5 other tumor types) were treated across multiple dose levels administered once daily (QD): 10 mg, 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 200/220 mg, 300 mg, and 400 mg. Patients had received a median of two prior lines of therapy (range 1–7) with standard of care appropriate for tumor type and stage.

As of the data cut-off, RMC-6236 demonstrated an acceptable safety profile that was generally well tolerated across dose levels. The most common treatment-related adverse events (TRAEs) were rash and GI-related toxicities that were primarily Grade 1 or 2 in severity. Of these, the reported Grade 3 TRAEs were rash (5%), stomatitis (2%), and diarrhea (1%). One previously reported Grade 4 TRAE occurred in a PDAC patient at the 80 mg QD dose level who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment, which resulted in treatment discontinuation. No safety signals were observed that indicated an elevated risk of hepatotoxicity, which has been reported for some KRAS^{G12C}(OFF) inhibitors.

RMC-6236 demonstrated dose-dependent increases in exposure at steady state with minimal accumulation after repeated daily oral dosing, which is compatible with once daily dosing. Clinical exposures achieved at dose levels of 80 mg QD and above were comparable to those that induced tumor regressions in preclinical xenograft models with KRAS^{G12X} mutations. Circulating tumor DNA (ctDNA) was assessed in 27 patients with detectable baseline plasma KRAS^{G12X} alleles and evaluable for changes in KRAS variant allele frequency (VAF) on-treatment. Molecular responses were observed across two tumor types (NSCLC and PDAC) and 4 different KRAS mutations (KRAS^{G12D}, KRAS^{G12V}, KRAS^{G12R}, and KRAS^{G12A}) with reductions in KRAS VAF consistent with anti-tumor activity. Three clinical case reports illustrated tumor regressions induced by RMC-6236 in patients with ovarian cancer (KRAS^{G12V}), NSCLC (KRAS^{G12D}) or PDAC (KRAS^{G12D}).

Phase 1/1b Trial of RMC-6291, RAS^{G12C}(ON) Inhibitor
The Phase 1/1b trial is a multicenter, open-label, dose-escalation and dose-expansion study designed to evaluate RMC-6291 as monotherapy in patients with advanced solid tumors harboring KRAS^{G12C} mutations. As of the October 5, 2023 data cut-off, a total of 63 patients (23 NSCLC, 33 CRC, 7 with other tumor types) received RMC-6291 at various doses, beginning at 50 mg once daily (QD), escalating to 100 mg QD, 200 mg QD, 100 mg twice daily (BID), 200 mg BID, 300 mg BID and 400 mg BID. Patients across all histologies had received a median of three prior therapies (range 1–7) with standard of care appropriate for tumor type and stage.

As of the data cut-off, RMC-6291 demonstrated preliminary evidence of clinical activity and an acceptable safety profile that was generally well tolerated across dose levels. The activity analysis included 37 patients (17 NSCLC, 20 CRC) who were evaluable for efficacy. Of the 10 NSCLC patients previously treated with a KRAS^{G12C}(OFF) inhibitor, 50 percent (n=5; one unconfirmed PR) achieved a partial response (PR) as best response, with a 100 percent disease control rate (DCR). Of the 7 NSCLC patients naïve to KRAS^{G12C}(OFF) inhibitors, 43 percent (n=3; two unconfirmed PRs) achieved a PR, with a 100 percent DCR. Among the 20 CRC patients naïve to KRAS^{G12C}(OFF) inhibitors, 40 percent (n=8; 3 unconfirmed PRs) achieved a PR as best response, with an 80 percent DCR. The median time to response was 1.3 months (range 1.1–4.1) and 1.4

months (range 1.2–4.1) for NSCLC and CRC patients, respectively. As of the data cut-off, no disease progressions had occurred among patients with an objective response, and 68 percent of all patients remained on treatment.

The most common TRAEs were QTc prolongation and GI-related toxicities that were primarily Grade 1 or 2 in severity. Grade 3 TRAEs were QTc prolongation (11.1%) and diarrhea (1.6%), and only one Grade 3 case was reported with a QTc ≥ 501 msec. All QTc prolongations were asymptomatic with no cardiac sequalae reported. No Grade 4 or 5 AEs or SAEs were reported. Nine patients (14.3%) were dose reduced due to TRAEs, and one patient (1.6%) discontinued treatment due to a Grade 3 QTc prolongation. No safety signals were observed that suggest an increased risk of hepatotoxicity, which has been reported for some $KRAS^{G12C}$(OFF) inhibitors.

Investor Webcast
Revolution Medicines will host an investor webcast on Sunday, October 22, 2023 at 12:30 p.m. Eastern Time to discuss the data presented at both the Triple Meeting and the 2023 European Society for Medical Oncology Congress, in addition to other clinical updates. To participate in the live webcast, participants may register in advance here: https://edge.media-server.com/mmc/p/eb8agxe6. A live webcast of the call will also be available on the Investors section of Revolution Medicines' website at https://ir.revmed.com/events-and-presentations. Following the live webcast, a replay will be available on the company's website for at least 14 days.

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}), RMC-6291 ($KRAS^{G12C}$) and RMC-9805 ($KRAS^{G12D}$) are currently in clinical development. Additional RAS(ON) Inhibitors in the company's pipeline include RMC-0708 ($KRAS^{Q61H}$) and RMC-5127 ($KRAS^{G12V}$) which are 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 company's development plans and timelines and its ability to advance its portfolio and R&D pipeline; progression of clinical studies and findings from these studies, including the tolerability and potential efficacy of the company's candidates being studied; the potential advantages and effectiveness of the company's clinical and preclinical candidates, including its RAS(ON) Inhibitors; the validation of the company's platform; potential differentiation between RMC-6291 and RAS(OFF) inhibitors; the company's goal of bringing therapies to cancer patients; and the company's expectations regarding the potential market size and size of the potential patient populations for the company's product candidates, if approved for commercial use. 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' 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 the company's 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 8, 2023, 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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