Revolution Medicines Provides Clinical Updates from its RAS(ON) Inhibitor Portfolio

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Compelling Phase 1/1b update on RMC-6236 monotherapy in second-line metastatic pancreatic ductal adenocarcinoma supports ongoing Phase 3 RASolute 302 clinical trial

Phase 1/1b proof-of-concept for RMC-6236 monotherapy in previously treated non-small cell lung cancer supports Phase 3 RASolve 301 clinical trial expected to be initiated in Q1 2025

Favorable initial safety profile for combination of pembrolizumab with either RMC-6236 or RMC-6291 supports continued evaluation in non-small cell lung cancer

Initial antitumor activity of RMC-6236 and RMC-6291 combination in heavily pretreated colorectal cancer supports RAS(ON) inhibitor doublet treatment strategy

REDWOOD CITY, Calif., Dec. 02, 2024 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for RAS-addicted cancers, today announced key clinical updates from its RAS(ON) inhibitor portfolio. The data to be presented during an investor webcast today at 8:00 a.m. Eastern Time (ET) will focus on updated clinical data from the Phase 1 RMC-6236 monotherapy study in pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC). In addition, new clinical data will be provided from several combination studies, including those evaluating RMC-6236 with pembrolizumab, RMC-6291 with pembrolizumab, and the first-of-its-kind RAS(ON) inhibitor doublet combination of RMC-6291 and RMC-6236.

“Our mission is to revolutionize treatment for patients with RAS-addicted cancers, and our ongoing progress is supported by the clinical milestones we continue to achieve in patients with a range of RAS mutant tumor types, stages of disease and lines of therapy,” said Mark A. Goldsmith, M.D., Ph.D., chief executive officer and chairman of Revolution Medicines. “We’ve now reported initial clinical validation of three differentiated RAS(ON) inhibitors, shown evidence of promising initial clinical activity and tolerability profiles in patients with three common, difficult-to-treat RAS-addicted tumors, and shared growing evidence of clinical impact delivered through three potential treatment paradigms – as monotherapy, in combination with pembrolizumab, and as RAS(ON) inhibitor doublets. With these compelling results, we are in a strong position to pursue an expansive set of late-stage development opportunities on behalf of patients with RAS-addicted cancers, beginning with the ongoing and pending pivotal trials.”

RMC-6236 Monotherapy Study
RMC-6236-001 is a multicenter, Phase 1/1b study designed to evaluate RMC-6236, a RAS(ON) multi-selective inhibitor, as monotherapy, in patients with advanced solid tumors. As of September 30, 2024, a total of 436 patients were treated across NSCLC (n=132) and PDAC and other solid tumors (n=304) cohorts. Patients were treated across a range of doses, from 10 mg to 400 mg once daily (QD).

PDAC Cohort
As an update to data reported at the EORTC-NCI-AACR (ENA) conference in October 2024, the company shared a new analysis of safety and activity data from the July 23, 2024 data cutoff date in patients with previously treated PDAC treated with a 300 mg QD dose, the same dose used in the ongoing RASolute 302 Phase 3 PDAC trial.

Key findings:

- In 76 patients with RAS mutant PDAC, RMC-6236 at 300 mg QD was generally well tolerated and showed an overall safety profile consistent with the results reported at ENA. No differentiated safety signals were observed.
    - The most common treatment-related adverse events (TRAEs) were rash and gastrointestinal (GI)-related toxicities that were primarily Grade 1 or 2 in severity. No Grade 3 or higher TRAEs were observed in greater than 10% of patients.
    - There were no treatment discontinuations due to TRAEs and the mean dose intensity was 89%.
- In 37 patients with 2L RAS mutant PDAC, RMC-6236 at 300 mg QD demonstrated compelling antitumor activity.
    - Patients with PDAC harboring a KRAS G12X mutation (n=22) achieved a median PFS of 8.8 months (95% confidence interval (CI), 8.5 months – not estimable (NE)), while the median OS was not estimable (95% CI, NE – NE). Patients with PDAC harboring any RAS mutation (n=37) achieved a median PFS of 8.5 months (95% CI, 5.9 months – NE), while the median OS was not estimable (95% CI, 8.5 months – NE).
    - The proportion of patients who remained alive six months after starting treatment with RMC-6236 was 100% and 97% in patients with PDAC harboring a KRAS G12X mutation and patients with PDAC harboring any RAS mutation, respectively.
    - The objective response rate (ORR) was 36% and 27% in patients with PDAC harboring a KRAS G12X mutation and patients with PDAC harboring any RAS mutation, respectively.

RASolute 302, the company’s randomized Phase 3 study of RMC-6236 versus standard of care chemotherapy in 2L patients with previously treated metastatic PDAC, is currently ongoing.

Next steps:

- Based on the encouraging monotherapy data update, the company aims to advance RMC-6236 into earlier lines of therapy for patients with metastatic PDAC.

NSCLC Cohort

As an update from a smaller initial cohort reported at ESMO 2023, data from a September 30, 2024 data cutoff date were reported for 124 patients with previously treated RAS mutant NSCLC who received RMC-6236 at clinically active doses in the range of 120 mg to 300 mg QD.

Key findings:

- In patients with previously treated NSCLC, RMC-6236 was generally well tolerated at doses of 120 mg to 220 mg QD, while the 300 mg QD dose demonstrated a higher frequency and severity of TRAEs.
    - In the 120 mg to 220 mg dose range, the most common TRAEs were rash and GI-related toxicities that were primarily Grade 1 or 2 in severity. No Grade 3 or higher TRAEs were observed in greater than 10% of these patients. In the 120 mg to 220 mg dose range, TRAEs leading to dose modification occurred in 41% of patients with 4% of patients discontinuing treatment due to TRAEs and the mean dose intensity was 88%.
- RMC-6236 at 120 mg to 220 mg QD demonstrated encouraging antitumor activity in the population of 40 efficacy-evaluable 2L or third-line (3L) patients with NSCLC who had received immunotherapy and platinum chemotherapy but had not received docetaxel.
    - These patients achieved a median PFS of 9.8 months (95% CI, 6 – 12.3 months), a median OS of 17.7 months (95% CI, 13.7 months – NE) and an ORR of 38%.

Next steps:

- The company expects to initiate RASolve 301, a randomized Phase 3 study of RMC-6236 versus docetaxel in patients with previously treated, locally advanced or metastatic RAS mutant NSCLC, in the first quarter of 2025.

RAS(ON) Inhibitor Combination Studies

RMC-6236 with Pembrolizumab
RMC-LUNG-101B is an arm of the Phase 1b study of RMC-6236 in combination with pembrolizumab, with or without chemotherapy, in patients with RAS mutant NSCLC. A total of 20 patients treated with RMC-6236 at 200 mg QD and pembrolizumab at the standard dose of 200 mg once every three weeks (Q3W) were evaluated as of an October 28, 2024 data cutoff date. The median duration of treatment for these patients was 2.3 months.

The combination of RMC-6236 with pembrolizumab was generally well tolerated and the safety profile was consistent with previously reported results for the individual agents. TRAEs of Grade 1 aspartate aminotransferase (AST) elevation were reported in two patients (10%) and a TRAE of Grade 2 AST elevation was reported in one patient (5%). A TRAE of Grade 1 alanine transaminase (ALT) elevation was reported in one patient (5%) and a TRAE of Grade 3 ALT elevation was reported in one patient (5%). The mean dose intensity for RMC-6236 was 97%.

Next steps:

- The company believes the data from this study support continued evaluation of the combination of RMC-6236 with pembrolizumab in 1L NSCLC patients.

RMC-6291 and RMC-6236 RAS(ON) Inhibitor Doublet
RMC-6291-101 is a Phase 1b study of RMC-6291 in combination RMC-6236 in patients with RAS G12C mutant solid tumors. The study has evaluated RMC-6291 at doses of 100 mg or 200 mg BID and RMC-6236 at a dose range of 100 mg to 300 mg QD. As of an October 28, 2024 data cutoff date, 74 patients were evaluated for safety with a median duration of treatment of 2.3 months.

The combination of RMC-6291 with RMC-6236 was generally well tolerated across all dose levels evaluated. The most common TRAEs were rash and GI-related toxicities that were primarily Grade 1 or 2 in severity. No Grade 3 or higher TRAEs were observed in greater than 5% of patients. One Grade 4 TRAE of hypokalemia was associated with Grade 3 diarrhea. TRAEs leading to dose interruption or reduction occurred in 30% and 10% of patients, respectively. The mean dose intensities for RMC-6291 and RMC-6236 were 95% and 92%, respectively.

A subset of efficacy-evaluable patients with colorectal cancer (CRC) who were previously treated with a KRAS(OFF) G12C inhibitor was evaluated for antitumor activity on treatment with RMC-6291 with RMC-6236. As reference values, the company also reported that the ORR for patients with CRC treated with RMC-6236 monotherapy at a dose of 300 mg daily in the RMC-6236-001 study as of a data cutoff date of September 30, 2024 was 9%, and the ORR for patients with CRC previously treated with a KRAS(OFF) G12C inhibitor who were subsequently treated with RMC-6291 monotherapy at a dose of 200 mg twice daily in the RMC-6291-001 study as of a data cutoff date of October 28, 2024 was 0%. In the combination study, patients with CRC who were previously treated with a KRAS(OFF) G12C inhibitor and who received their first doses of the two study drugs at least 8 weeks prior to data cutoff were included in the analyses (n=12). The ORR was 25%, including one patient with an unconfirmed complete response, and the DCR was 92%. The median treatment duration was 2.3 months.

Next steps:

- The company believes the data from this combination study support continued development of RAS(ON) doublets in a broad range of tumor types and earlier lines of therapy.

RMC-6291 with Pembrolizumab
RMC-LUNG-101A is an arm of the Phase 1b study of RMC-6291, a RAS(ON) G12C-selective inhibitor, in combination with pembrolizumab, with or without chemotherapy, in patients with RAS G12C mutant NSCLC. A total of 15 patients treated with RMC-6291 at 200 mg twice daily (BID) and pembrolizumab at the standard dose of 200 mg Q3W were evaluated as of an October 28, 2024 data cutoff date. As of this date, 47% of these patients had been on treatment for 60 days or more.

The combination of RMC-6291 with pembrolizumab was generally well tolerated and the safety profile was consistent with previously reported results for the individual agents. A TRAE of Grade 1 AST elevation was reported in one patient (7%) and a TRAE of Grade 1 ALT elevation was reported in one patient (7%). There were no TRAEs of Grade 2 or higher AST or ALT elevations reported. The mean dose intensity for RMC-6291 was 98%.

Next steps:

- The company believes the three pairwise combinations of RMC-6291 with RMC-6236, RMC-6236 with pembrolizumab and RMC-6291 with pembrolizumab justify investigation of the triplet combination of RMC-6291 and RMC-6236 with pembrolizumab as a potential chemotherapy-

sparing option for patients with 1L NSCLC.

Investor Webcast
The Revolution Medicines investor webcast will begin at 8:00 a.m. Eastern Time. A link to participate in the live webcast can be accessed here and is also available on the Events and Presentations section of Revolution Medicines' investor 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. The company's RAS(ON) inhibitors RMC-6236, a RAS(ON) multi-selective inhibitor, RMC-6291, a RAS(ON) G12C-selective inhibitor, and RMC-9805, a RAS(ON) G12D-selective inhibitor, are currently in clinical development. Additional development opportunities in the company's pipeline focus on RAS(ON) mutant-selective inhibitors, including RMC-5127 (G12V), RMC-0708 (Q61H) and RMC-8839 (G13C), in addition to RAS companion inhibitors RMC-4630 and RMC-5552.

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 expected timing and progression of clinical studies and findings from these studies, including the safety, tolerability and antitumor activity of the company's product candidates alone or in combination with other therapies, and the durability of these results; the late-stage development opportunities the company plans to pursue; the expected timing of initiation of the company's Phase 3 RASolve 301 clinical trial; the company's aim to advance RMC-6236 into earlier lines of therapy for patients with PDAC; the company's plans to develop RAS(ON) doublets in a broad range of tumor types and earlier lines of therapy; the company's continued evaluation of the combination of RMC-6236 with pembrolizumab in 1L NSCLC patients; and the company's plans to study the triplet combination of RMC-6291, RMC-6236 and pembrolizumab. 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' current stage of development, the process of designing and conducting preclinical studies and clinical trials, risks that the results of prior clinical trials may not be predictive of future clinical trials, clinical efficacy, or other future results, 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 impacting the company, and the effects on the company's business of global events, such as international conflicts or global pandemics. 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 the company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 6, 2024, and its future periodic reports to be filed with the SEC. Except as required by law, the company 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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