Revolution Medicines Announces Publication Demonstrating Robust Anti-Tumor Activity of RAS(ON) Inhibitors in Preclinical Models of Refractory KRAS-Mutated Non-Small Cell Lung Cancer

July 11, 2024

Original research published in *Cancer Discovery* reveals a RAS(ON) multi-selective inhibitor exhibited robust anti-tumor activity alone or in combination with a RAS(ON) G12C-selective inhibitor in preclinical models of difficult-to-treat KRAS-mutated non-small cell lung cancer (NSCLC)

Results also highlight that, in contrast to mutant-selective RAS inhibition, broad-spectrum, reversible RAS-GTP inhibition with a RAS(ON) multi-selective inhibitor alone drove durable anti-tumor activity in these models with infrequent resistance occurrence and the potential for emergence of rare persister, slow cycling cells

REDWOOD CITY, Calif., July 11, 2024 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for patients with RAS-addicted cancers, today announced the publication of a peer-reviewed research paper in *Cancer Discovery.* The scientific paper demonstrates that the RAS(ON) multi-selective inhibitor RMC-7977 (a preclinical tool compound representative of the investigational drug candidate RMC-6236) exhibited robust and durable anti-tumor activity in multiple preclinical models of KRAS-mutated NSCLC. The data show this activity was further enhanced in the doublet combination with a RAS(ON) G12C-selective inhibitor RMC-4998 (a preclinical tool compound representative of the investigational drug RMC-6291), in preclinical models of KRAS G12C-mutated NSCLC. These findings are the result of original, collaborative research between scientists at Revolution Medicines and The University of Texas MD Anderson Cancer Center.

Oncogenic RAS proteins drive up to 30 percent of all human cancers, most notably NSCLC, pancreatic ductal adenocarcinoma and colorectal cancer. RAS G12 mutations, such as G12D, G12V and G12C, predominate in these RAS-addicted cancers. Approved RAS-targeted cancer therapies target only one RAS mutation, KRAS G12C, which is present in approximately 13 percent of NSCLC. There remains a large unmet medical need for improved clinical outcomes with KRAS G12C-selective inhibitors and for extending therapy options to patients harboring KRAS non-G12C-driven tumors.

The paper highlights that direct RAS inhibition with a RAS(ON) multi-selective inhibitor monotherapy, alone or in combination with a RAS(ON) G12C-selective inhibitor, elicited rapid, deep and sustained tumor regressions and significantly prolonged time to tumor doubling in preclinical models of refractory KRAS G12C-mutated NSCLC. The combination dramatically improved anti-tumor activity as compared to RAS(ON) multi-selective inhibitor monotherapy and elicited cures (defined as recurrence free survival following treatment withdrawal) in all of the preclinical models bearing alterations in genes associated with the subsets of KRAS G12C-mutated NSCLC (e.g. KEAP1 and SMARCA4). The RAS(ON) multi-selective inhibitor overcame acquired resistance to RAS(OFF) and RAS(ON) G12C-selective inhibitors in these models of advanced KRAS G12C-mutated NSCLC, further underscoring the robust activity of this inhibitor.

The paper also unveils a conserved mucinous regenerative program, apparent upon treatment cessation, that may support long-term tumor cell persistence in the context of sustained RAS pathway inhibition. Characterization of this emergent population of persister cells, a rare slow cycling group of cancer cells that may endure despite ongoing inhibitor treatment, provides insights into potential therapeutic strategies that could prevent them from driving recurrent tumor growth.

“RAS-addicted cancers are widely known for being resistant to current cancer therapies and recent studies have highlighted mechanisms of clinical resistance to RAS(OFF) G12C-inhibitors. We evaluated the anti-tumor activity of a broad spectrum RAS(ON) multi-selective inhibitor alone and in combination with a RAS(ON) G12C mutant-selective inhibitor in models of clinically challenging subsets of KRAS G12C-mutated NSCLC. Given the novel mechanism of action of these inhibitors, directly targeting oncogenic RAS, a key question was whether primary, adaptive or acquired resistance mechanisms would emerge following treatment,” said Jan Smith, Ph.D., Chief Scientific Officer of Revolution Medicines. “These encouraging preclinical data provide a strong rationale for our ongoing combination study of RMC-6236 as a doublet with RMC-6291 in patients with advanced KRAS G12C-mutated cancers.”

The investigational oral drug RMC-6236 is a RAS(ON) multi-selective inhibitor designed to treat patients with cancers driven by a wide range of common RAS mutations. Revolution Medicines is currently evaluating RMC-6236 as monotherapy in a Phase 1/1b trial in patients with advanced solid tumors harboring G12X, G13X and Q61X mutations (NCT05379985). Following promising preliminary data in this Phase 1/1b study, planning is underway to initiate pivotal studies of RMC-6236 as monotherapy in PDAC and NSCLC. RMC-6236 is also being evaluated in combination with pembrolizumab with or without chemotherapy in patients with advanced RAS-mutated solid tumors (NCT06162221) and in combination with RMC-6291, the company’s investigational RAS(ON) G12C-selective inhibitor, for patients with advanced KRAS G12C-mutated solid tumors (NCT06128551).

The publication, entitled, “Mechanisms of response and tolerance to active RAS inhibition in KRAS-mutant NSCLC,” is available online at: https://aacrjournals.org/cancerdiscovery/article-abstract/doi/10.1158/2159-8290.CD-24-0421/746287/Mechanisms-of-response-and-tolerance-to-active-RAS?redirectedFrom=fulltext.

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, 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 include its RAS(ON) mutant-selective inhibitors RMC-5127 (G12V), RMC-0708 (Q61H) and RMC-8839 (G13C), in addition to RAS companion inhibitors 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 potential advantages of Revolution Medicines’ preclinical and preclinical candidates, including their potential efficacy, durability,

tolerability and combination potential; the company's current and planned clinical studies, including the company's ongoing combination study of RMC-6236 as a doublet with RMC-6291; unmet medical needs; and potential therapeutic strategies related to persister cells. 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 studies and clinical trials, risks that the results of prior preclinical models or studies 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, and the effects on the company's business of global events, such as international conflicts or pandemics. For a further description of the risks and uncertainties that could cause actual results to differ from those anticipated in the 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 8, 2024, 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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