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Investigational Inhibitor of Active RAS Shows Clinical Promise

The therapy uses a different mechanism than approved KRAS G12C inhibitors and targets multiple RAS mutations beyond KRAS G12C

BOSTON – RMC-6236, an investigational oral therapeutic that inhibits the active state of multiple RAS variants, was tolerated and exhibited activity in patients with various cancers, according to phase I clinical trial results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 11-15, 2023.

"KRAS is mutated in approximately 30% of cancers, and the most frequent mutations replace the glycine at position 12 (G12) with another amino acid in cancers such as pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and colorectal cancer (CRC)," explained Alexander Spira, MD, PhD, the CEO and clinical director of NEXT Oncology-Virginia, a co-director of the Virginia Cancer Specialists Research Institute, and a clinical assistant professor at Johns Hopkins University.

"The KRAS protein cycles between an inactive and active state, and cancer-causing KRAS mutations can drive KRAS into the active state," Spira said, adding that increased signaling of wild-type RAS can also be a driver of tumors.

The KRAS G12C-selective inhibitors sotorasib (Lumakras) and adagrasib (Krazati), which are approved for the treatment of certain NSCLCs, work by binding the inactive form of KRAS G12C and blocking it from becoming active. However, these drugs are effective exclusively against the KRAS G12C variant and have been associated with treatment resistance driven by various mechanisms.

Spira and colleagues evaluated a different type of KRAS inhibitor, RMC-6236, a RAS^{MULTI} inhibitor that targets the active form of RAS proteins with a wide range of different mutations, preventing these proteins from carrying out their pro-tumor effects.

"Preclinical studies indicated that targeting the active form of KRAS can mitigate some of the important resistance mechanisms associated with existing inhibitors and, therefore, may lead to deeper and more durable tumor regression," Spira explained.

Unlike sotorasib and adagrasib, RMC-6236 targets KRAS proteins harboring any mutation at the G12 position, not just G12C. This may allow RMC-6236 to be effective against a wider array of cancer types, Spira noted.

"No direct inhibitors are approved for cancer patients with KRAS mutations beyond G12C, which represents a significant unmet medical need across several cancer types, including NSCLC, PDAC, and CRC," Spira said, adding that RMC-6236 also targets wild-type KRAS and KRAS with mutations at other positions, such as the glycine located at position 13 (G13) and the glutamine at position 61 (Q61).

To evaluate dosing, safety, and clinical activity of RMC-6236, clinical investigators, including Spira and colleagues, are participating in a phase I clinical trial, which includes patients with previously treated advanced solid tumors harboring KRAS G12 mutations (currently excluding G12C mutations).

As of the data extract on September 11, 2023, a total of 131 patients had been treated with RMC-6236 in this trial. The majority of patients had pancreatic cancer and NSCLC; the remaining patients had colorectal cancer and other solid tumors. Approximately 50% of patient cancers harbored a KRAS G12D mutation; other mutations included KRAS G12V, G12R, G12A, and G12S, consistent with the epidemiology of RAS mutations in human cancers, Spira noted.

RMC-6236 demonstrated dose-dependent pharmacokinetics compatible with once-daily dosing and achieved exposures predicted to induce tumor regression. Marked reduction in multiple KRAS mutant alleles in the circulating tumor DNA from patient blood samples across tumor types was indicative of anti-tumor activity. Radiographic partial responses (per RECIST 1.1) were observed across several tumor types and KRAS mutants at clinically active dose levels.

Three illustrative case studies of treated patients exhibiting partial responses were presented: KRAS G12V-mutated ovarian cancer, KRAS G12D-mutated NSCLC, and KRAS G12D-mutated PDAC.

Median duration of treatment at the time of the data extraction was 2.27 months (range: 0.2–14 months). The most common treatment-related adverse events (TRAE) were grade 1 or 2 rash or gastrointestinal-related toxicities, such as nausea, vomiting, or diarrhea. The most common grade 3 TRAE was rash. One patient experienced a grade 4 large intestine perforation at the site of an invasive tumor that reduced in size while on treatment. Most adverse events observed in the trial were manageable with standard supportive care, Spira noted.

“The results from this study are encouraging and demonstrate that we can target the active form of KRAS mutants across several tumor types and KRAS genotypes with an oral treatment that is well tolerated and delivers antitumor activity,” said Spira. “RMC-6236 has the potential to become the first inhibitor to target active KRAS proteins harboring a variety of mutations beyond G12C.”

A limitation of the study is that, as a phase I dose-finding trial, it is designed to primarily assess safety and determine the optimal dose for further evaluation. Additional clinical testing will be needed to evaluate drug efficacy and safety and to compare it to current standards of care.

The study is sponsored by Revolution Medicines, which developed RMC-6236.

Spira holds a leadership role with NEXT Oncology-Virginia and holds stock in Eli Lilly. Spira has received honoraria from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol-Myers Squibb, and Bayer. Spira has served consulting or advisory roles with Incyte, Amgen, Novartis, Mirati Therapeutics, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Regeneron, Eli Lilly, Black Diamond Therapeutics, Sanofi, Array BioPharma, AstraZeneca/MedImmune, Merck, Bristol-Myers Squibb, and Blueprint Medicines. Spira has received research funding from LAM Therapeutics, Regeneron, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Incyte, Abbvie, Ignyta, Takeda, Macrogenics, CytomX Therapeutics, Astex Pharmaceuticals, Loxo, Arch Therapeutics, Gritstone Bio, Plexxicon, Amgen, Daiichi Sankyo, ADC Therapeutics, Janssen Oncology, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Alkermes, Revolution Medicines, Medikine, Black Diamond Therapeutics, BluPrint Oncology, Nalo Therapeutics, Scorpion Therapeutics, and ArriVent Biopharma.

Abstract

Title: Preliminary safety and pharmacokinetic profiles of RMC-6236, a first-in-class, RAS-selective, tri-complex RASMULTI(ON) inhibitor in patients with KRAS mutant solid tumors on the Phase 1 trial RMC-6236-001

Background: RMC-6236 is an oral RASMULTI(ON) tri-complex inhibitor that is selective for the active, GTP-bound state of both mutant and wild-type variants of the canonical RAS isoforms. RMC-6236 binds to cyclophilin A, which is abundantly expressed in normal tissues and tumors, resulting in a binary complex that potently binds to RAS(ON) to form a tri-complex, blocking downstream signaling. Preclinical studies with RMC-6236 demonstrated deep and sustained regressions across multiple RASMUT tumor types at well tolerated doses, particularly tumors harboring KRAS glycine-12 substitutions (KRASG12X). **Methods:** Patients with previously treated, advanced KRASG12X mutant solid tumors were enrolled at escalating doses of single agent RMC-6236 administered once daily (QD). **Results:** As of May 11, 2023, 54 patients received RMC-6236 at dose levels from 10 to 220 mg QD. The majority of patients had pancreatic cancer (26 [48%]), non-small cell lung cancer (13 [24%]), or colorectal cancer (10 [19%]). The most common (≥10% of patients) treatment-related adverse events (TRAEs) were rash and gastrointestinal (GI)-related toxicities that were all Grade 1 or 2 in severity. Most rashes were acneiform (35%) or maculopapular (13%), consistent with known on-target rash presentation from other RAS pathway inhibitors. Rash frequency, but not severity, was dose-dependent. One patient required a dose reduction due to Grade 2 acneiform rash. The most common GI-related toxicities were nausea (32%), diarrhea (19%), and vomiting (15%) that were manageable with standard supportive care. There were two Grade ≥3 TRAEs in patients with pancreatic cancer: Grade 4 large intestine perforation at the site of an invasive tumor that reduced in size on treatment, and Grade 3 pancreatitis reported at the time of disease progression. Thirty-one patients (57%) remain on treatment, and 23 (43%) discontinued, including 17 (31%) due to progressive disease (PD) per RECIST v1.1, 2 (4%) due to clinical progression, and other reasons due to adverse event (Grade 4 large intestine perforation), death (due to PD), investigator's decision, or patient withdrawal (1 patient each). RMC-6236 exhibited dose-dependent increases in exposure in patients with no apparent accumulation in the blood following repeated daily dosing. At 220 mg QD, exposure to RMC-6236 was within range of the preclinical exposures in mice that demonstrated significant tumor regressions. Preliminary evidence of anti-tumor activity, including partial responses per RECIST v1.1, was observed in patients across several tumor types and dose levels. Molecular responses were observed with reduction in circulating tumor DNA of the KRAS-mutated allele and other somatic mutations consistent with inhibition of mutant RAS by RMC-6236. **Conclusions:** RMC-6236 is safe and well tolerated at doses that induce anti-tumor activity in patients with tumors harboring KRASG12X mutations and has favorable pharmacokinetics with oral dosing. A recommended phase 2 dose has not yet been determined and dose escalation is ongoing.

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