UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 13, 2023

REVOLUTION MEDICINES, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-39219**	**47-2029180**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification Number)**

700 Saginaw Drive
Redwood City, California 94063
(Address of principal executive offices, including Zip Code)

Registrant's telephone number, including area code: (650) 481-6801

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	RVMD	The Nasdaq Stock Market LLC (Nasdaq Global Select Market)

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On October 13, 2023, Revolution Medicines, Inc. (the "Company") provided the following pipeline updates.

RMC-6236

The Company reported updated safety and pharmacokinetic data for RMC-6236, its RAS^{MULTI}(ON) Inhibitor.

In the Company's ongoing RMC-6236-001 Phase 1/1b trial, 131 patients treated across nine dose cohorts ranging from 10 mg daily to 400 mg daily were evaluable for safety and tolerability as of a data cut-off date of September 11, 2023 (the "RMC-6236 Data Cut-off Date"). 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. Of the 131 patients, 69 had pancreatic ductal adenocarcinoma ("PDAC"), 47 had non-small cell lung cancer ("NSCLC"), 10 had colorectal cancer ("CRC") and five had other tumor types. All of these patients have been previously treated with standard of care and/or other regimens, with an overall median of two prior lines of therapy (with a range of one to seven prior lines of therapy).

As of the RMC-6236 Data Cut-off Date, the Company observed that RMC-6236 demonstrated an acceptable safety profile that was generally well tolerated across dose levels in patients with solid tumors (Table 1). Median duration of treatment as of the RMC-6236 Data Cut-off Date was 2.27 months (range: 0.2–14). The most common treatment-related adverse events ("TRAEs") were rash and gastrointestinal ("GI")-related toxicities that were primarily Grade 1 or 2 in severity. One previously reported Grade 4 TRAE occurred in a patient with PDAC treated at 80 mg 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 fatal TRAEs were observed. Two patients discontinued study treatment due to death: one patient with PDAC (120 mg) died due to progressive disease; one patient with NSCLC (200 mg) died due to an unknown cause reported as unrelated to RMC-6236. No safety signals were observed that indicated an elevated risk of hepatotoxicity, which has been reported for some KRAS^{G12C}(OFF) inhibitors.

Table 1. RMC-6236-001: Select treatment-related adverse events

Total (N=131)

Maximum severity of treatment-related AEs (TRAEs)	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
TRAEs occurring in ≥10% of patients, n (%)					
Rash*	57 (44)	29 (22)	6 (5)	—	92 (70)
Nausea	41 (31)	14 (11)	—	—	55 (42)
Diarrhea	32 (24)	9 (7)	1 (1)	—	42 (32)
Vomiting	27 (21)	9 (7)	—	—	36 (28)
Stomatitis	10 (8)	9 (7)	2 (2)	—	21 (16)
Fatigue	12 (9)	4 (3)	—	—	16 (12)
Other select TRAEs, n (%)					
ALT elevation	6 (5)	1 (1)	1 (1) ‡	—	8 (6)
AST elevation	6 (5)	—	1 (1) ‡	—	7 (5)
Electrocardiogram QT prolonged	1 (1)	—	—	—	1 (1)
TRAEs leading to dose reduction†, n (%)	—	9 (7)	2 (2)	—	11 (8)
TRAEs leading to treatment discontinuation, n (%)	—	—	—	1 (1)	1 (1)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; PD, progressive disease; TRAEs, treatment-related adverse events.

‡ Post-data extraction, the Grade 3 ALT and AST elevations were associated with biliary obstruction and reported as unrelated to RMC-6236.

* Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, dermatitis psoriasiform, erythema and rash erythematous.

† The most common TRAE leading to dose reduction was rash (acneiform or maculopapular); there were no reductions at doses ≤80 mg.

As of the RMC-6236 Data Cut-off Date, the Company observed that RMC-6236 demonstrated dose-dependent increases in exposure at a steady state with minimal accumulation after repeated daily oral dosing, which is compatible with once-daily dosing. Clinical exposures achieved at once daily dose levels of 80 mg 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 four 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 ($KRAS^{G12D}$).

RMC-6291

The Company reported preliminary safety and anti-tumor data for RMC-6291, its RAS^{G12C}(ON) Inhibitor.

In the Company's ongoing RMC-6291-001 Phase 1/1b trial, 63 patients treated across seven dose cohorts ranging from 50 mg daily to 400 mg twice daily were evaluable for initial safety and tolerability as of a data cut-off date of October 5, 2023 (the "RMC-6291 Data Cut-off Date"). Of these patients, 23 had NSCLC, 33 had CRC and seven had other tumor types. All of these patients were previously treated with standard therapy, with an overall median of three prior lines of therapy (with a range of one to seven prior lines of therapy).

As of the RMC-6291 Data Cut-off Date, the Company observed that RMC-6291 demonstrated an acceptable safety profile that was generally well tolerated across dose levels (Table 2). Tolerability was generally consistent across tumor types. The most common TRAEs were QTc prolongation and GI-related toxicities that were primarily Grade 1 or 2 in severity. All QTc prolongations were asymptomatic with no cardiac sequalae reported. No treatment-related Grade 4 or 5 AEs or serious AEs ("SAEs") were reported. No safety signals were observed that suggest an increased risk of hepatotoxicity, which has been reported for some $KRAS^{G12C}$(OFF) inhibitors.

Table 2. RMC-6291-001: Select treatment-related adverse events

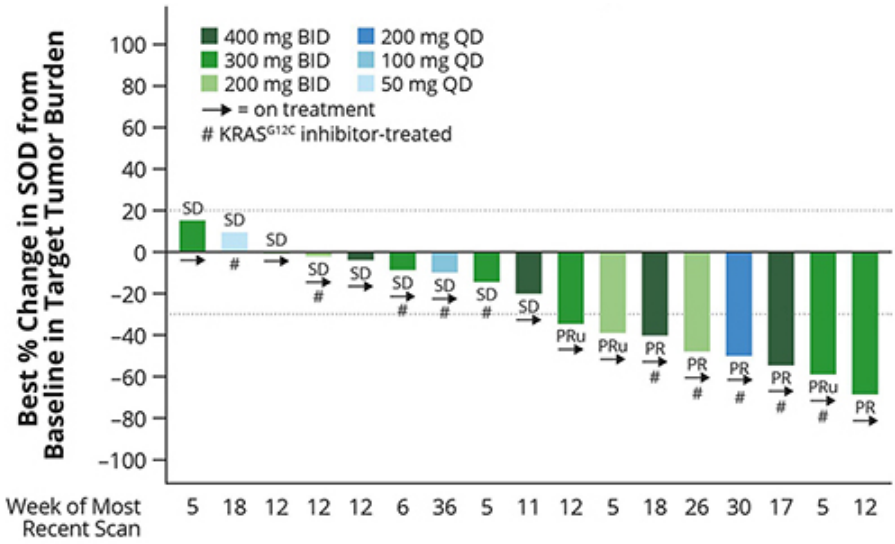
Total (N=63) **Maximum Severity of Treatment-Related AEs (TRAEs)**	**Grade 1**	**Grade 2**	**Grade 3**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)				
Diarrhea	10 (16)	7 (11)	1 (2)	18 (29)
Nausea	14 (22)	3 (5)	—	17 (27)
ECG QT prolonged	8 (13)	1 (2)	7 (11)	16 (25)
QTcF* ≥ 501 ms	—	—	1 (2)	—
Fatigue	4 (6)	4 (6)	—	8 (13)
Vomiting	6 (10)	2 (3)	—	8 (13)
AST increased	7 (11)	—	—	7 (11)
TRAEs leading to dose reduction, n (%)	—	1 (2)	8 (13)	9 (14)
TRAEs leading to treatment discontinuation, n (%)	—	—	1 (2)	1 (2)

As of the RMC-6291 Data Cut-off Date, the Company observed that RMC-6291 was orally bioavailable and demonstrated dose-dependent plasma pharmacokinetics. Reduction in ctDNA of the $KRAS^{G12C}$ allele across doses was observed to correlate with clinical response.

As of the RMC-6291 Data Cut-off Date, RMC-6291 demonstrated preliminary evidence of clinical activity in patients with $KRAS^{G12C}$-mutant NSCLC previously treated with or naïve to a $KRAS^{G12C}$(OFF) inhibitor (Figure 1).

Figure 1. RMC-6291-001: Change in tumor burden from efficacy-evaluable patients with NSCLC previously treated with or naïve to a KRAS^{G12C}(OFF) inhibitor)

Evaluable for Efficacy* (N=17)



Data Extracted October 5, 2023.

CR, complete response; PR, confirmed partial response; PRu, unconfirmed partial response; SD, stable disease; ORR objective response rate; DCR, disease control rate; RECIST, Response evaluation criteria in solid tumors.

* All treated patients who received a first dose of RMC-6291 at least eight weeks prior to the data extract date.

Tumor response per RECIST 1.1 for the patients reflected in Figure 1 is summarized below (Table 3).

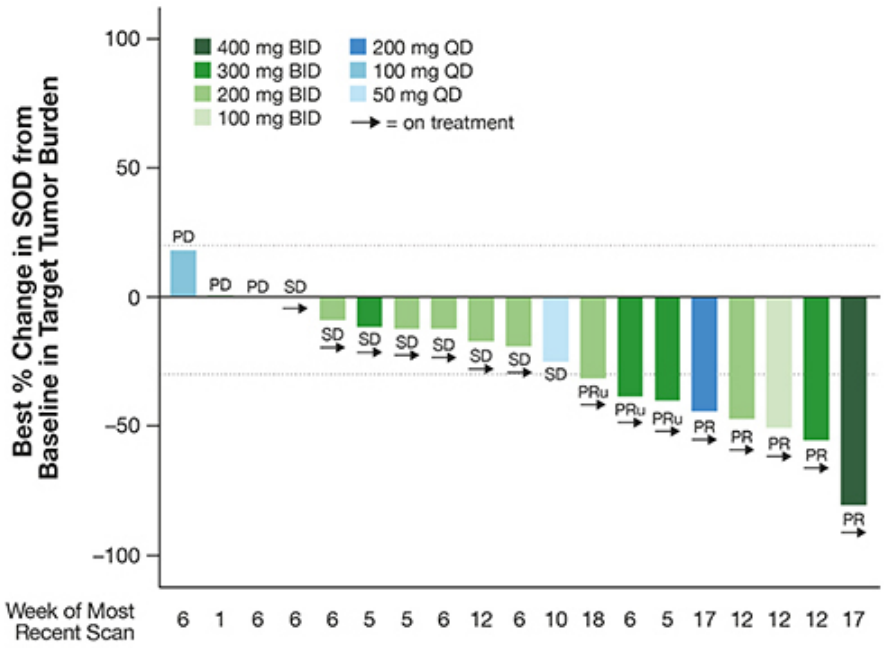
Table 3. RMC-6291-001: Tumor Response per RECIST for efficacy-evaluable patients with NSCLC previously treated with or naïve to a KRAS^{G12C}(OFF) inhibitor

Tumor Response (per RECIST 1.1)		
Best Overall Response, n (%)	**Prior G12Ci (n=10)**	**Naïve to G12Ci (n=7)**
Partial response†	5 (50)	3 (43)
Stable disease	5 (50)	4 (57)
Progressive disease	—	—
ORR, n (%)	5 (50)	3 (43)
DCR (CR+PR+SD), n (%)	10 (100)	7 (100)

† Partial response includes five confirmed and three unconfirmed.

As of the RMC-6291 Data Cut-off Date, RMC-6291 also demonstrated preliminary evidence of clinical activity in patients with KRAS^{G12C}-mutant CRC who were naïve to treatment with a KRAS^{G12C}(OFF) inhibitor (Figure 2).

Figure 2. RMC-6291-001: Change in tumor burden from efficacy-evaluable patients with CRC that were naïve to treatment with a $KRAS^{G12C}$(OFF) inhibitor



Data Extracted October 5, 2023.

* All treated patients who received first dose of RMC-6291 at least eight weeks prior to the data extract date.

Tumor response per RECIST 1.1 for the patients reflected in Figure 2 is summarized below (Table 4).

Table 4. RMC-6291-001: Tumor Response per RECIST for efficacy-evaluable patients with CRC that were naïve to treatment with a $KRAS^{G12C}$(OFF) inhibitor

Tumor Response (per RECIST 1.1)	
Best Overall Response, n (%)	N=20‡
Partial response†	8 (40)
Stable disease	8 (40)
Progressive disease	4 (20)
ORR, n (%)	8 (40)
DCR (CR+PR+SD), n (%)	16 (80)

† Partial Response includes five confirmed and three unconfirmed.
‡ One patient had progressive disease due to a new lesion; target lesion measurements were not available.

The Company believes the reported data provide preliminary evidence of differentiation of RMC-6291 from $KRAS^{G12C}$(OFF) inhibitors.

RMC-5127

The Company has selected RMC-5127, which is designed as an oral covalent tri-complex inhibitor of $KRAS^{G12V}$(ON), as a development candidate.

Forward-Looking Statements

This Current Report on Form 8-K contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. Any statements in this report that are not historical facts may be considered “forward-looking statements,” including, without limitation, statements regarding the scope, progress and results of developing the Company’s product candidates, and conducting clinical trials. 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 global events and other macroeconomic conditions. 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 the Company in general, see the Company’s Quarterly Report on Form 10-Q filed with the SEC on August 8, 2023, 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.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

REVOLUTION MEDICINES, INC.

Date: October 13, 2023

By: /s/ Mark A. Goldsmith
Mark A. Goldsmith, M.D., Ph.D.
President and Chief Executive Officer