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A Phase 2, Open-Label, Multicenter Study of the Combination of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer Subjects with *KRASG12C* Mutation After Failure of Prior Standard Therapies

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Statistical Analysis Plan

A Phase 2, Open-Label, Multicenter Study of the Combination of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies

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Labcorp Drug Development Study ID: 000000219213
Sponsor: Revolution Medicines, Inc.

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Approvals

The undersigned agree that all required reviews of this document are complete and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

Approved by
Labcorp Lead Statistician Approval

Signature	Date

Shahnaz D. Hawkins, Sr. Principal Biostatistician, Labcorp Drug Development Inc.

Revolution Medicines Inc. Approval:

DocuSigned by: Yunming Mu 16412F6366A14A1...	20-Apr-2023
Signature	Date

Yunming Mu, Executive Director, Head of Biostatistics, Revolution Medicines Inc.

List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ATC	Anatomical Therapeutic Chemical
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BIW	Twice weekly
BMI	Body mass index
BRAF Class 3	Class 3 type mutations in BRAF
BRAT	Banana, rice, apples, toast
BUN	blood urea nitrogen
C1, Cx, etc.	Cycle 1, Cycle x, etc.
C1D1, CxDx, etc.	Cycle 1 Day 1, Cycle x Day x, etc.
CI	Confidence interval
CNS	Central nervous system
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRO	Contract research organization
CS	Clinically significant
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
ctRNA	Circulating tumor RNA
D1, Dx, etc	Day 1, Day x, etc.

Abbreviation	Term
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HEENT	Head, eyes, ears, nose, and throat
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
ISMC	Internal Safety Monitoring Committee
KRAS	Kirsten rat sarcoma viral oncogene homolog
KRASKRAS^{G12C}	Kirsten rat sarcoma viral oncogene homolog; KRAS with a mutation at codon 12, which encodes glycine (G) to cysteine (C);
LLN	Lower limit of normal
LSLV	Last subject last visit
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
mTPI-2	Modified toxicity probability interval-2
MUGA	Multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NF1	Neurofibromin 1

Abbreviation	Term
NF1LOF	Mutations in NF1 predicted to result in loss of function
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non–small cell lung cancer
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PO	Oral(ly)
PK	Pharmacokinetic
PR	Partial response
PS	Performance status
PT	Preferred Term
PTT	Partial thromboplastin time
QD	Once Daily
QTc	Corrected QT interval
QTcF	QT interval corrected using Frederica's formula
RAS-MAPK	RAS Mitogen-Activated Protein Kinase
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	Recommended phase 2 dose
RPED	Retinal pigment epithelial detachment
RTK	Receptor tyrosine kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation, Stable Disease
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

1. Introduction

This statistical analysis plan (SAP) has been developed after review of the clinical study protocol RMC4630-03 (Original Protocol Version 1.0 dated 21 June 2021; Version 2.0 22 July 2021, Version 3.0 21 March 2022; Version 4.0 21 November 2022 and electronic case report form (eCRF).

This SAP describes the planned statistical methods for evaluating the efficacy, safety, tolerability, and PK of RMC-4630 in combination with sotorasib data for this study. Additional details of variable definitions are included in the supplemental Standard Programming Specification document. The planned table, figure, and listing (TFL) to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E3 guideline Structure and Content of Clinical Study Reports, ICH E8 guideline General Considerations for Clinical Trials, and ICH E9 guideline Statistical Principles for Clinical Trials.

The document history is presented in Appendix A.

2. Protocol Details

2.1 Study Objectives

Primary objectives are:

- To evaluate the antitumor effects of RMC-4630 and sotorasib in locally advanced or metastatic NSCLC subjects with *KRAS*^{G12C} mutation with and without co-existing genetic aberrations in specific genes such as *STK11/LKB1*, *KEAP1*, and *PIK3CA* after failure of prior standard therapy

Secondary objectives are:

- To characterize the safety, tolerability, and PK of RMC-4630 in combination with sotorasib for subjects with *KRAS*^{G12C} mutant NSCLC after failure of prior standard therapy
- To further characterize efficacy of RMC-4630 in combination with sotorasib as assessed by DOR, DCR, PFS, and OS in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy

Exploratory objectives are to:

- To explore PK relationships with safety and/or efficacy endpoints
- To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples

2.2 Study Design

2.2.1 Overall Study Design and Plan

This is a phase 2 multicenter, open-label study evaluating the efficacy, safety, tolerability, and pharmacokinetics (PK) of RMC-4630 in combination with sotorasib in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy. The overall study schema is illustrated in Figure 1. The study will be conducted at approximately 40 clinical sites globally and is expected to enroll up to approximately 46 subjects.

Prior to enrollment, all subjects will undergo screening to determine study eligibility. Eligibility will be assessed based on inclusion and exclusion criteria (Protocol Sections 5.1 and 5.2, respectively) and prior/local genomic testing reports from a tumor biopsy or plasma sample. Information on the presence of any genotypic aberrations in the tumor will be collected for all subjects based on prior/local genomic testing reports. Mutation testing results for all subjects must have been obtained in a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) certified laboratory and collected within 3 years of the subject's study enrollment. See Protocol Appendix 9 for details of genotypic mutations required for enrollment. Subjects may remain in the study, regardless of the results of central laboratory testing, unless other exclusionary criteria are met, or the subject withdraws consent.

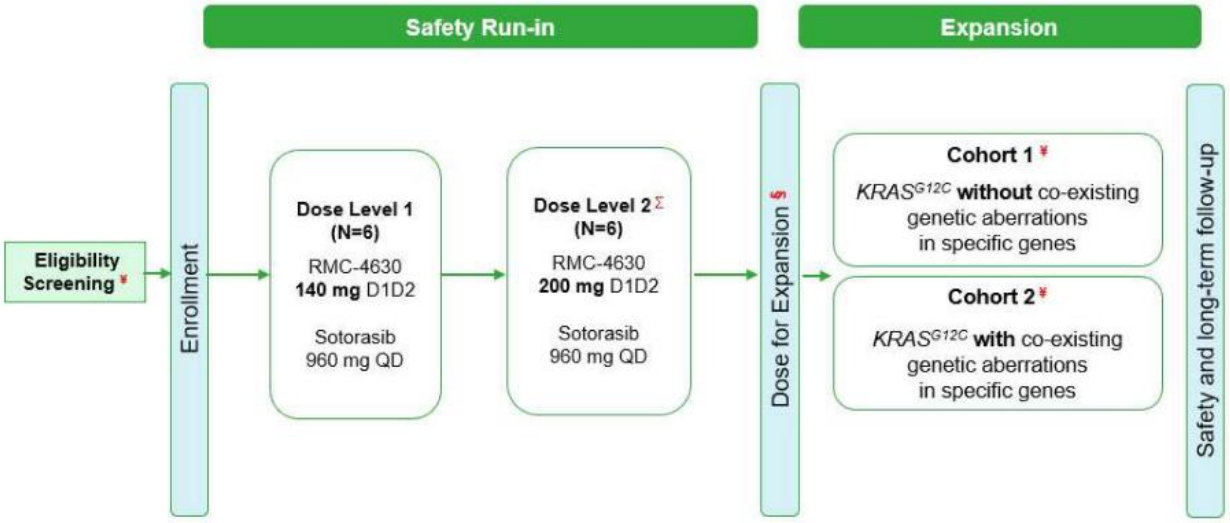
This Phase 2 study will have a safety run-in period where RMC-4630 will be administered at a starting dose of 140 mg on D1D2 of each week in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) and sotorasib 960 mg QD in a 21-day cycle. Subjects will be evaluated for dose -limiting toxicities (DLTs) (Protocol Section 8.4). The decision to escalate the RMC-4630 dose to 200 mg on D1D2 of each week in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) will be guided by a modified toxicity probability interval 2 (mTPI-2) algorithm (Protocol Appendix 11) and made by the Dose Committee. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled into one or both dose cohorts for the purpose of dose optimization before selecting the final expansion dose. Expansion may commence as soon as the expansion dose has been selected from either CodeBreaK 101C or this study, whichever occurs first. The Sponsor may proceed directly to dose expansion without completing the safety run-in period. The combination dose for expansion will be determined by the Sponsor after taking into consideration the totality of available data from CodeBreaK 101C and the cumulative data from this study.

The study will enroll a total of approximately 46 subjects globally. Subjects will be categorized into 1 of 2 cohorts.

- Cohort 1 will be the primary cohort of this study and will consist of *KRAS*^{G12C} NSCLC subjects **without** potential genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (see detailed list in Protocol Appendix 9).
- Cohort 2 will consist of *KRASG12C* NSCLC subjects **with** co-existing genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (Protocol Appendix 9).

The overall study design schema is shown in Figure 1 below.

Figure 1 RMC-4630-03 Study Schema



Abbreviations: ctDNA = circulating tumor deoxyribonucleic acid; D1D2 = Day 1 and Day 2 of *each week* in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle); *KRASG12C* = *KRAS* with a mutation at codon 12, which encodes glycine (G) to cysteine (C); mTPI-2 = modified toxicity probability interval-2; QD = once daily.

¥ Eligibility for study entry will be based on existing genomic reports from a qualified or validated test. Retrospective ctDNA may identify computation (s) that may shift subjects from Cohort 1 to Cohort 2.

Σ The starting dose is 140 mg on D1D2 of each week in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) and escalation to 200 mg on D1D2 of *each week* in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) will be guided by an mTPI-2 algorithm (Protocol Appendix 11) and made by the Dose Committee. At the Sponsor's discretion, new subjects enrolling on this trial may be treated at the lower sotorasib dose of 240 mg QD in combination with RMC-4630 instead of 960 mg in combination with RMC-4630 (Protocol Table 4 and Table 5).

§ Expansion in this study may commence as soon as the expansion dose has been selected from either CodeBreaK 101C or RMC-4630-03, whichever occurs first. The Sponsor may proceed directly to dose expansion without completing the safety run-in period. The combination dose for expansion in this study will be determined by the Sponsor after taking into consideration the totality of available data from both CodeBreaK 101C and cumulative data from this study. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled into one or both dose levels for the purpose of dose optimization to inform final expansion dose selection.

2.2.2 Duration of Treatment

Subjects will be permitted to remain on study treatment until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met (Protocol Section 7.1), whichever occurs first. Subjects who discontinue treatment will return to the clinical site for an EOT visit within 30 days after last dose of study treatment.

2.2.3 Long-Term Follow-Up Period

For subjects who discontinue treatment and do not withdraw consent, there will be a Lost to Follow-up (LTFU) period for clinical evaluation of disease status and survival. Subjects will be followed via telephone every 3 months (±2 weeks) for assessment of survival and documentation of anticancer treatment. LTFU Subjects will be followed until withdrawal of consent, subject death, or EOS (Protocol Section 4.4), whichever occurs first.

2.2.4 Duration and End of Study (EOS)

The study duration is approximately 2 years. The EOS is defined as the date of LSLV or 12 months after the last subject receives the first dose of study treatment, whichever occurs first.

2.2.5 Intervention After the End of the Study

Subjects who are on treatment at the EOS and are deriving clinical benefit from RMC-4630 and sotorasib will be considered for enrollment in a separate extended-use or roll-over study. These subjects should rollover to the separate study without interruption of treatment and should complete EOT assessments listed in the SoA (Protocol Table 1) prior to treatment on Day 1 of the extended-use or roll-over study.

2.2.6 Internal Safety Monitoring Committee (ISMC)

An Internal Safety Monitoring Committee (ISMC) will be used to monitor the safety of RMC-4630 and sotorasib combination therapy throughout the study. The ISMC is RMC-4630 program specific and will review emergent safety data at regular intervals for all subjects during the trial in conjunction with data from other active RMC-4630 clinical trials. Additional details are provided in Protocol Section 8.3.6.2.

2.3 Sample Size Determination

Up to a total of 46 subjects will be enrolled into this study. Approximately 6 to 12 subjects will be enrolled during the safety run-in portion of the study. Initially, up to 6 subjects will be enrolled and treated at the dose of 140 mg BIW on D1D2 of each week in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) in combination with sotorasib at 960 mg QD. An additional 6 subjects may be enrolled to receive RMC-4630 200 mg BIW on D1D2 of each week in a 21-day cycle (i.e., Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) in combination with sotorasib at 960 mg QD, if a decision is made to increase the RMC-4630 dose from 140 mg to 200 mg. After completion of the safety run-in (DLT clearance) of both dose levels, additional patients may be enrolled for the purpose of dose optimization to inform the selection of the final expansion dose. Expansion may commence as soon as the final expansion dose has been selected. Approximately 34 to 40 subjects will be enrolled for dose optimization and dose expansion.

With a total sample size of 46 subjects, the probability of observing at least 1 AE with an incidence rate of 5% is at least 90%.

The ORR will be reported by dose level pooling subjects from safety run-in and dose optimization (if applicable) and expansion. It's anticipated that approximately 20 to 40 subjects will be treated at the final expansion dose depending on the actual number of subjects enrolled during safety run-in and/or dose optimization. For the final expansion dose, with 20 and 40 subjects, the lower bound of the one-sided 80% exact CI will be above 33.7% and 37.3% respectively if the observed response rate is 45%.

The mutational status of each subject and, thus, placement into Cohort 1 or 2 (Protocol Section 4.1) will be determined based on the historic genomic reports and later might be adjusted based on ctDNA analysis results collected at baseline. Therefore, the sample size for one or both cohorts will depend on the distribution of mutational status.

3. Endpoints

Primary Endpoints

- ORR as assessed per RECIST v1.1

Secondary Endpoints

- Incidence, nature, and severity of TEAEs, SAEs, clinically significant changes in laboratory tests, ECGs, and vital signs
- Trough and approximate peak concentrations of RMC-4630 and sotorasib
- DOR, DCR, and PFS as assessed per RECIST v1.1, and OS

Exploratory Endpoints

- Sotorasib and RMC-4630 exposure/safety and exposure/efficacy relationships
- Quantification of biomarker expression (protein, RNA, and DNA levels) as appropriate in ctDNA and archival tumor tissues (or fresh, if archival tumor is not available)

4. Pharmacokinetic (PK)

See 7.8 of this SAP.

5. Analysis Populations

Treated Population
Includes all subjects who have taken at least one dose of study treatment.

Efficacy-Evaluable Population
Includes all subjects with measurable disease at baseline, who have taken at least one dose of study treatment and (1) underwent one post-baseline response assessment or (2) who died or (3) had clinical progression prior to the first post-baseline response assessment.

DLT-Evaluable Population
Includes all subjects enrolled during safety lead-in in the treated population who have received at least 80% of planned dose of sotorasib and at least 4 of 6 doses of RMC-4630 in Cycle 1 and have been observed for safety assessments for the full 21 days of the DLT evaluation period. Subjects who experience a DLT within the DLT period will be considered DLT evaluable regardless of the amount of study treatment received or completion of the observation period.

6. Data Handling

6.1 Study Day and Visit Windows

Day 1 is defined as the date of first dose of study treatment. For days on or after the first dose of study treatment:

Study day = non-missing date of assessment/event - date of first treatment + 1

For days before the first dose of study treatment:

Study day = non-missing date of assessment/event - date of first treatment
(one day prior to date of the first dose will be considered 'Day -1')

For all analysis populations, all data will be analyzed using nominal scheduled study visits as defined in the SoA, i.e., scheduled visits. The only exception is for clinical safety laboratory evaluations, the analysis of shifts from baseline to worst post-baseline will use all scheduled and unscheduled visits within the study phase.

No visit windows will be applied for summary and analysis.

6.2 Handling of Missing Data and Dates of Events

All safety analyses will be conducted on the observed data unless otherwise mentioned. No imputation of values for missing data will be performed except that missing or partial start and end dates of adverse events used for the assessment of treatment emergence status of an AE, study day of onset, and duration of the AE (if applicable) and concomitant medication. Missing and / or incomplete dates for AEs and concomitant medications are imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the AE or concomitant medication is "Ongoing".

The detailed imputation algorithms will be specified at programming specifications. Refer to Section 7.6 for handling of missing efficacy data.

7. Statistical Methods

7.1 General Principles

Formal statistical hypothesis testing will not be performed.

Analysis of safety data will be presented by the initial combination dose level. Safety analyses will be presented for each cohort separately and for the overall study population. For efficacy analyses will be presented by the initial combination dose level. Efficacy analyses will be presented for Cohort 1 and Cohort 2 separately, and for the overall study population.

All summary tables will include data from scheduled assessments, unless otherwise specified. A final analysis will be performed at the EOS as defined in Section 2.2.4.

Confidence intervals (CI) will be two-sided and will use and 95% coverage, unless specified otherwise.

Subject listings of data (scheduled and unscheduled) from the eCRFs, external source and derived variables will be presented by dose level.

Study Day: In all the subject listings, the study day of all complete dates as defined in Section 5.1 will be presented.

Baseline: Unless stated otherwise, baseline is defined as the last non-missing assessment prior to the first dose of either study drug (RMC-4630 or sotorasib).

SAS® Version 9.4 or higher will be the statistical software package used for all data analysis and presentation.

The Tables of Contents of Tables, listings, and figures (TLFs) a document external to this SAP. Mock of TLF shells will be created in a separate document.

7.1.1 Handling of Data Quality Issues due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Related Restrictions

Due to Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and related restrictions, there is a high risk for impact to data integrity, with the recognized potential for:

- Missed visits, caused by, for example:
  - Subject unable to travel to site due to restrictions, the need to quarantine, or SARS-CoV-2 infection
  - Subject unwilling to go to site due to fear of SARS-CoV-2 infection
  - Site postponing subject's visit due to investigator not being available (e.g., if they have been dispatched to hospital handling SARS-CoV-2 infections)
- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to SARS-CoV-2 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (e.g., data might be categorized into 2 analysis groups, with and without SARS-CoV-2 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Revolution Medicines, Inc. in advance and identified in the CSR.

7.2 Subject Disposition and Data Sets Analyzed

All subject's disposition data will be summarized for by the initial combination dose level and overall using treated population. The summary will include following:

- number of subjects in each analysis population,
- number of subjects discontinuing treatment with primary reason for treatment discontinuation,
- number of subjects discontinuing study with primary reason for study discontinuation, and
- number of subjects continued to long term follow-up period
- time on study (month) calculated as (study exit date - first treatment date + 1) /30.4375, censored using earlier of data cut-off date and death date
- time on each treatment (months) calculated as (last treatment date – first treatment date + 1) /30.4375, censored using data cut-off date.

The percentages will be calculated based on total number of subjects in each dose level. The percentages for primary reason for treatment or study discontinuation will be calculated based on total number of subjects who discontinued the treatment and/or the study at each dose level.

Data listing of disposition information will also be provided.

7.3 Protocol Deviations

Important protocol deviations employed in database deviation report that could potentially affect the interpretation of the safety, efficacy, PK, or PD data will be identified by the review team prior to database lock. All Coronavirus Disease of 2019 (COVID-19) related deviations are also recorded in the protocol deviation document.

All major protocol deviations will be summarized by the initial combination dose level and overall using treated population. The count of unique subjects with at least one major protocol deviation as well as the number of subjects in each protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all important protocol deviations, including the description of the deviation, deviation category of 'major', and date of deviation will be provided.

In addition, a listing of the subjects affected by COVID-19 and the type of COVID-19 disruption will be provided for the treated population if applicable.

Any additional details will be documented and added prior to database lock.

7.4 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographic, baseline characteristics, medical history, and prior/concomitant medications will be summarized by dose level and overall using the treated population.

7.4.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics include, but not limit to the following parameters and will be summarized using descriptive statistics:
All subject's demographic and baseline characteristics will be summarized by dose level and overall using all treated population.

- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Years since initial cancer diagnosis
- Number of previous systemic cancer therapies

The following demographic and baseline characteristics variables will be summarized using count and percentage:

- Age (<=65 or > 65 years)
- Sex
- Age by Sex (Female: <=65 or > 65 years, Male: <=65 or > 65 years)
- Ethnicity
- Race
- Childbearing potential (females only)
- Smoking status (current smoker, past smoker, never smoked)

- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- PD-L1 expression at study entry
- PD-L1 Expression (TPS <1%, TPS 1% - 49%, TPS >=50%)
- History of CNS involvement
- Disease stage at study entry
- Brain Metastasis at Baseline (Yes/No)
- Liver Metastasis at Baseline (Yes/No)

The summary will also include count and percentage of all subjects with the following genotypic mutations based on the historic genomic reports and ctDNA analysis results collected at baseline:

- Cohort 1: Only *KRAS*^{G12C} (without any potential genetic modifiers)
- Cohort 2: *KRAS*^{G12C} co-occurring with STK11/LKB1, KEAP1, PIK3CA, BRAF Class 1/2/unclassified, ATRX, or BRCA2

Data listing of demographic and baseline characteristics information will be provided.

7.4.2 Medical History

Medical history terms will be coded using the MedDRA® (Medical Dictionary for Regulatory Activities), Version 25.0 or later. Medical history will be summarized by dose level and overall using treated population by system organ class (SOC) and preferred term (PT). For the table summary, a subject will only be presented once for each level of summarization.

Subject listings of medical history, non-cancer related surgical history, and cancer related surgical history will also be provided.

7.4.3 Cancer History

Cancer history data, previous systemic cancer therapy, previous radiation therapy may be summarized for the treated population.

Subject listings of cancer history, previous systemic cancer therapy, previous radiation therapy will also be provided.

7.4.4 Surgical Procedures

Subject listings of any on-study surgical procedures and any blood transfusions will be provided.

7.4.5 Previous and Concomitant Medications

All prior and concomitant medications will be coded using WHODrug Global, B3 March 2018 or later.

Prior medications are defined as those medications that started and ended prior to Day 1, the first exposure to study drug (RMC-4630 and sotorasib combined). Concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose. If a medication start or end date is fully missing, and it is unclear as to whether the medication is

prior or concomitant, it will be assumed that it is concomitant. If a medication start date or end date is partially missing, then the date will be imputed based on rules described in Section 5.2

Summary of concomitant medication will be presented by WHO Anatomical Therapeutic Chemical (ATC) and preferred term (PT) by the initial combination dose level and overall using treated population. A subject will only be counted once per ATC and once per PT within a dose level.

Listings for prior and concomitant data and protocol specified prohibited medications will be provided.

7.5 Study Drug Exposure and Compliance

Duration of exposure and relative dose intensity will be calculated and summarized with descriptive statistics using treated population.

Number and percent of subjects experienced dose change (dose missed, reduced, and discontinued), and primary reason for dose change will also be summarized by dose level and overall.

Listing of drug exposure from dose administration log including derived cumulative planned dose, cumulative actual dose, and relative dose intensity for each subject will be provided. Listing of drug dispenses including lot/kit number, and list of change in dose assignment/frequency for each treatment will also be provided.

7.6 Efficacy Analyses

The efficacy endpoints of ORR, DCR, and DOR will be based on the treated population, and will be summarized by the initial combination dose level. As supportive analyses, these efficacy endpoints will also be summarized for the efficacy-evaluable population. PFS and OS will be summarized on the all-treated population. Efficacy analyses will also be presented by Cohort 1 and Cohort 2 at the expansion dose level.

Handling of Missing Efficacy Data

- For analyses of binary endpoints, subjects among the analysis population who have not achieved the outcome of interest by the time of analysis will be considered a non-responder for the analysis.
- For time to event endpoints, subjects without post-baseline assessments will be censored at the date of the first dose of study drug.

7.6.1 Primary Efficacy Analysis

Objective Response Rate (ORR)

The primary endpoint ORR is defined as the proportion of subjects who have achieved either Complete Response (CR) or Partial Response (PR) per RECIST1.1. A CR or PR should be confirmed by a repeat assessment no less than 28 days.

ORR and the corresponding 95% two-sided exact binomial confidence interval using the Clopper-Pearson method will be presented.

Frequency and percentages for individual best overall response (BOR) which includes CR, PR, Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) per RECIST v1.1 (see Appendix B) will also be summarized.

In addition, summary of best percent change from baseline in tumor size by best overall response using efficacy evaluable population will be presented. A waterfall and spaghetti plots of percent change from baseline for sum of diameters (SOD) by best overall response will also be presented.

7.6.2 Secondary Efficacy Analysis

Disease Control Rate (DCR)
DCR is defined as the proportion of subjects who achieve a CR or PR or SD per RECIST v1.1. A CR or PR should be confirmed by a repeat assessment no less than 28 days, and SD requiring the minimum duration of 5 weeks from initiation of first dose of study drug ((i.e., at least 35 days between treatment start and scan date qualifying the subject for a BOR of SD).

DCR and the corresponding 95% two-sided exact binomial confidence interval using the Clopper-Pearson method will be presented.

Duration of Response (DOR)
DOR is defined as the interval from the first documentation of CR or PR to first documentation of definitive disease progression or death due to any cause, whichever occurs first.

Subjects who are still alive and free from progression at the time of data cutoff date, or lost to follow-up, or discontinued from the study or initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. Subjects who never achieve a response (PR or better) will be excluded from the analysis of DOR. (Refer to censoring rule document)

DOR = (date of event/censor – first date of confirmed CR or PR + 1) / 30.4375.

The Kaplan-Meier method will be used to estimate DOR curves and corresponding quartiles. The Kaplan-Meier median will be calculated with a two-sided 95% confidence intervals. If the number of responders is less than 5, DOR data will be provided in a subject listing.

A Swimmer plot of response and duration of treatment will be presented.

Progression Free Survival (PFS)
PFS is defined as the interval from the first dose of study treatment to documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first.

For subjects who are still alive and free from progression at the time of data cutoff date, or lost to follow-up, or discontinued from the study, or initiated subsequent anticancer therapy, PFS will be censored at the last adequate tumor assessment.

For subjects with PD or death after two or more missing consecutive scheduled assessments, or if a subject initiated subsequent anticancer therapy before the PD date or death prior to first post-baseline scan, PFS will be censored at the last tumor assessment visit prior to the occurrence of the consecutive missing visits or prior subsequent anticancer therapy respectively.

Subjects who do not have post-baseline evaluable tumor assessment, PFS will be censored at day 1.

PFS = (date of event/censor – date of first dose of study drug + 1) / 30.4375.

PFS will be summarized for the all-treated population. The Kaplan-Meier method will be used to estimate PFS curves and corresponding quartiles. The Kaplan-Meier median will be calculated with a 2-sided 95% confidence intervals.

7.6.3 Subgroup Analysis

Efficacy analyses of ORR (confirmed and unconfirmed), DCR, PFS, and OS by demographics and baseline characteristics subgroups will be performed for all treated and efficacy evaluable populations.

Other efficacy analyses may also be performed in subgroups, as applicable, using the same analysis methods as described for the overall population.

Overall Survival (OS)
OS is defined as the interval from the first dose of study drug to death, from any cause. Subjects who are not known to have died will be censored at the last known alive date. (Refer to censoring rule document).

OS = (date of event/censor – date of first dose of study drug + 1) / 30.4375.

OS will be summarized on the all-treated population. The Kaplan-Meier method will be used for analyses of OS. The Kaplan-Meier median with 95% two-sided confidence intervals will be estimated.

7.7 Safety Analyses

Safety endpoints of the study are the incidence, nature, and severity of treatment-emergent adverse events (TEAEs), SAEs, clinical laboratory tests, vital signs, and ECGs.

Adverse events (AEs) will be collected from the date that informed consent was signed. Verbatim terms for each AE will be coded using MedDRA Version 25.0 or later and graded per the NCI CTCAE Version 5.0 or later. Treatment-emergent adverse event (TEAE) is defined as those AEs with an onset on or after the date of the first dose of study intervention and within 30 days of last known dose of study intervention. Treatment-related AEs are treatment-emergent AEs reported as related to RMC-4630 or sotorasib.

All AE summaries will be presented for the initial combination dose level and overall using the treated population.

Safety Stopping Rules
During dose expansion after the final expansion dose has been selected, evaluation of all Grade 4 or higher treatment-related adverse event rates will be conducted to assess if the unacceptable toxicity threshold has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data. After reviewing the totality of data from both CodeBreaK 101C and cumulative data from this study, one of the following actions may be taken:

1. Terminate the study
2. Amend the protocol to potentially improve the benefit/risk for subjects (e.g., increase safety monitoring, modify dose/schedule, mandate premedication)
3. Continue dose expansion without any changes

The stopping rules use a Bayesian approach to pause the enrollment if the posterior probability is ≥ 80% that the Grade 4 or higher treatment-related adverse event rate is greater than 20%. The stopping boundaries shown in Table 1 assume a prior distribution of Beta (0.4, 1.6). The operating characteristics with the pre-specified batch size of 10 new subjects are summarized in Table 2.

Table 1: Stopping Boundary by Number of Subjects

Number of Subjects Treated	Number if Subjects with Grade 4 or Higher Treatment Related Adverse Events to Halt Enrollment
10	≥ 4
20	≥ 6
30	≥ 9
40	Expansion Complete

Table 2: Operating Characteristics of Stopping Rules

True Grade 4 or Higher Treatment-Related Adverse Event Rate	Probability of Early Stopping of Dose Expansion	Average Dose Expansion Sample Size
0.1	2.1%	39
0.15	9.7%	38
0.2	25.8%	34
0.25	47.7%	29
0.3	69.2%	23

7.7.1 Analyses of Clinical Safety Laboratory Results

All clinical laboratory evaluations including clinical chemistry, hematology, coagulation and urinalysis, and pregnancy tests will be performed per Protocol SoA.

For each test, baseline is defined as the last non-missing value prior to first dose of the study treatment.

All post-baseline summaries will include results collected on or after the date of the first dose of study intervention and within 30 days of last known dose of study intervention. Shifts from baseline to worst post-baseline CTCAE Version 5.0 or later grade (including unscheduled visits) will be presented by frequency and percentage for select laboratory parameters. For those parameters where worst is an increase or a decrease from baseline, separate summaries will be presented.

Time to onset of and duration of first post-baseline hematologic abnormalities of hemoglobin decreased, platelet count decreased and neutrophil count decrease will be summarized for each grade using descriptive statistics.

Listings of all subjects with clinically significant abnormal results including concurrent elevated ALT ≥3 × upper limit of normal (ULN) or AST ≥3 × ULN AND bilirubin >2 × ULN or ALT ≥3 × ULN and concurrent INR >1.5 at any time post-baseline will be presented over time.

Listings of all laboratory values (hematology, chemistry, coagulation, urinalysis, pregnancy tests, and other screening test results) including results from unscheduled visits will be provided. The

listing will flag all out of normal ranges values and will include change from baseline for each post-baseline measurement (where applicable).

Adverse Events of Clinical Interest (ECI)

Adverse events of Clinical interest are defined based on sponsor pre-defined standardized MedDRA queries (SMQs) extracted using MedDRA preferred terms as listed in RMC-4630 Events of Clinical Interest document.

ECI will be summarized by category, subcategory, and preferred term. In addition, time to onset (days) of treatment-emergent ECI of any grade, grade ≥3 and their associated durations of resolved events will be summarized for treatment arm, each category and sub-category (where applicable) using descriptive statistics. Time to first occurrence of treatment-emergent ECI is calculated as time from first dose date of study treatment (RMC-4630 or sotorasib) – AE start date + 1. Duration of resolved adverse events is calculated as the AE end date – AE start date + 1.

7.7.2 DLTs

All DLT assessments will be performed on the DLT-evaluable population. Number and percentages of subjects who experienced DLT will be summarized by preferred term (PT) by descending order of incidence of PT.

A data listing of DLT events will also be provided.

7.7.3 Adverse Events

The overview summary will include number of events; number and percentage of participants for categories of AEs; grade ≥3 TEAEs, treatment-related AEs, grade ≥3 treatment-related TEAEs, SAEs, treatment-related SAEs, AEs leading to study drug discontinuation, dose level reduction, interruption, or dose change, adverse events of clinical interests (ECI), and AEs leading to death.

The number and percentage of subjects who experienced AEs will also be summarized by preferred term (PT) by descending order of incidence of PT. In addition, AEs and SAEs will also be summarized by system organ class (SOC) and PT by descending order of incidence of SOC, and descending order of incidence of PT within each SOC. The summaries will include the following for any grade and grade ≥3 if applicable:

- Overview Summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT
- Summary of TEAEs related to RMC-4630 by PT
- Summary of TEAEs related to sotorasib by PT
- Summary of TEAEs related to RMC-4630 or sotorasib by PT
- Summary of TEAEs by maximum severity and PT
- Summary of TEAEs related to RMC-4630 or sotorasib by maximum severity and PT
- Summary of serious TEAEs by SOC and PT
- Summary of non-Serious TEAEs by SOC and PT

- Summary of serious TEAEs by PT
- Summary of serious TEAEs related to RMC-4630 by PT
- Summary of serious TEAEs related to sotorasib by PT
- Summary of serious TEAEs related to RMC-4630 or sotorasib by PT
- Summary of TEAEs leading to discontinuation of RMC-4630 by PT
- Summary of TEAEs leading to discontinuation of sotorasib by PT
- Summary of TEAEs leading to discontinuation of RMC-4630 or sotorasib by PT
- Summary of TEAEs leading to discontinuation of RMC-4630 or sotorasib by SOC and PT
- Summary of TEAEs leading to dose reduction of RMC-4630 by PT
- Summary of TEAEs leading to dose reduction of sotorasib by PT
- Summary of TEAEs leading to reduction of RMC-4630 or sotorasib and PT
- Summary of TEAEs leading to reduction of RMC-4630 or sotorasib by SOC and PT
- Summary of TEAEs leading to dose interruption of RMC-4630 by PT
- Summary of TEAEs leading to dose interruption of sotorasib by PT
- Summary of TEAEs leading to dose interruption of RMC-4630 or sotorasib by PT
- Summary of TEAEs leading to dose interruption of RMC-4630 or sotorasib by SOC and PT
- Summary of TEAEs leading to dose modification of RMC-4630 by PT
- Summary of TEAEs leading to dose modification of RMC-4630 by SOC and PT
- Summary of TEAEs leading to dose modification of sotorasib by PT
- Summary of TEAEs leading to dose modification of sotorasib by SOC and PT
- Summary of TEAEs leading to dose modification of RMC-4630 or sotorasib by PT
- Summary of TEAEs leading to dose modification of RMC-4630 or sotorasib by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of ECI by category, sub-category, and PT
- Summary of time to onset of ECI by category and sub-category

Treatment-related AEs include those events considered by the investigator to be possibly, probably, or definitely related to study drug (RMC-4630 or sotorasib). AEs with missing relationship status will be classified as related.

If the same PT is reported multiple times for a subject within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject has multiple reported events within the same SOC, that SOC will only be reported once. If a subject experiences the same AE with more than one severity, or with more than one relationship to study intervention, the most severe rating or the stronger causal relationship to study drug(s) will be assigned to the event. Any missing severity or outcome will not be imputed and classed as unknown/missing.

Subject listings of all reported AEs, SAEs, AEs leading to dose reduction, treatment interruption, treatment discontinuation from the study, and death will be provided. The listings will be sorted by subject ID, study day, SOC/PT/verbatim term, and severity grade.

Deaths

Summary listing of reported death by any cause will be provided. The number and percentage of subjects experiencing deaths (all-cause) and causes of deaths will be summarized, and will also be categorized as death within or beyond 30 days of last dose of study drugs which occurs later.

7.7.4 Vital Signs, Weight and Height

Data listing of vital signs data (systolic and diastolic blood pressure, pulse rate, pulse oximetry, respiratory rate, temperature, weight, and height at screening) including change from baseline value will be provided. Select vital sign parameters will be summarized using actual values and changes from baseline at each post-baseline scheduled visit using descriptive statistics.

7.7.5 Electrocardiograms (ECG) and QTcF Interval

Baseline is defined as the last non-missing measurement on or prior to the first dose of study drug.

The QTcF and ECG overall interpretation (normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS]) will also be summarized for baseline and change from baseline to EOT [expressed as Improvement, No Change, and Deterioration] by dose level, where:

- Improvement = Abnormal CS to Abnormal NCS/Normal or Abnormal NCS to Normal;
- Deterioration = Normal to Abnormal NCS/CS, Normal/Abnormal NCS to Abnormal CS
- No change = Normal to Normal, Abnormal NCS to Abnormal NCS, Abnormal CS to Abnormal CS.

In addition, the QTcF values for baseline, actual values and changes from baseline at each post baseline visit will be summarized by dose level using descriptive statistics.

The frequency and percentage of the maximum post-baseline QTcF values classified in accordance with the ICH E14 boundaries will be presented:

Table 1: QTcF / QTcB Interval ICH E14 Boundaries

QTcF / QTcB Interval	Criteria (msec)
Maximum Observed QTcF / QTcB interval	<=450 msec >450 msec >480 msec >500 msec
Maximum Change from baseline in QTcF / QTcB interval	<=30 msec >30 to <= 60 msec >60 msec

A listing of all ECG data including individual and calculated mean of triplicate measurements, derived change from baseline will be provided using the treated population, along with demographic information of age and sex. Any value outside the clinical reference range will be flagged.

7.7.6 Echocardiograms/Multigated Acquisition Scans

Echocardiogram or multi-gated acquisition results will be presented in a data listing. In addition to descriptive statistics of observed data, the number and percent of subject with LVEF values below 50% will be presented.

7.7.7 Eastern Clinical Oncology Group Performance Status (ECOG PS)

Data listing of ECOG PS results will be provided.

7.7.8 Physical Examinations

Data listing of physical examinations data will be provided.

7.8 Pharmacokinetics Analyses

Concentrations of RMC-4630 and sotorasib will be summarized descriptively by timepoint as part of the main CSR. Concentrations of RMC-4630 may be used for population PK analysis and presented in a separate report. PK of RMC-4630 may be used for integrated E-R analysis and reported separately.

7.9 Exploratory Analyses

Biomarker exploratory analyses may be described in a separate analysis plan and may be summarized in a report separate from the clinical study report.

8. Interim Analyses

No formal interim analysis will be conducted. However, as this is an open-label study, several analyses may be conducted at specific points during the study as well as at the end of the study.

9. Deviations from Statistical Analysis Plan

Any deviations from this statistical plan will be described and justified in the final clinical study report.

10. Significant Changes from the Protocol-specified Analyses

There have been no other changes in analyses from those defined in the protocol.

11. References

1 Loboda A, Nebozhyn M, Klinghoffer R, et al. A gene expression signature of RAS pathway dependence predicts response to PI3K and RAS pathway inhibitors and expands the population of RAS pathway activated tumors. BMC Med Genomics. 2010; 3:26. doi: 10.1186/1755-8794-3-26

2 Riviere MK, Yuan Y, Dubois F, Zohar S. A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. Pharmaceutical statistics. 2014;13(4):247-57. doi: 10.1002/pst.1621.

3 ICH. Statistical Principles for Clinical Trials, Guideline E9, 1998. Available at https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

4 CPMP. Points to Consider on Missing Data. EMEA: London, 2001. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-missing-data_en.pdf

5 Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

6 Guidance for Industry ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 12 May 2005.

7 SAS Institute Inc., Cary, NC, USA.

12. Appendices

Appendix A1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	21 March 2022	V3.0
Protocol	21 November 2022	V4.0
eCRF	20 January 2023	V6

Appendix A2. Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	18 April 2023	NA; the first version, based on Protocol V4.0

Appendix B. Safety Laboratory Tests: Identifying Worst Values

Laboratory Test	Direction of Interest for Worst Case Values
HEMATOLOGY	
RBC Count	Low
Hemoglobin	Low
Hematocrit	Low
Platelet Count	Low
MCV	Low
MCH	Low
WBC Count	Low and High
Neutrophils	Low and High
Lymphocytes	Low and High
Monocytes	High
Eosinophils	High
Basophils	High
CHEMISTRY	
Sodium	Low and High
Potassium	Low and High
Chloride	Low
Bicarbonate	Low
BUN (Blood Urea Nitrogen)	Low and High
Creatinine	High
Glucose (non-fasting)	Low and High
Total Protein	Low
Albumin	Low
Phosphate	Low
Calcium	Low and High
Magnesium	Low
Uric Acid	High
Direct Bilirubin	High
LIVER SAFETY TESTS	
GGT	High
ALT (SGPT)	High
AST (SGOT)	High
Total Bilirubin	High
ALP	High
COGULATION TESTS	
INR	High
PT	High
aPTT	High
PTT	High