Official Title:

A Phase 1b/2, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 with Cobimetinib in Adult Participants with Relapsed/Refractory Solid Tumors and a Phase 1b Study of RMC-4630 with Osimertinib in Participants with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

NCT Number:

03989115

Document Date:

November 20, 2020

Protocol Title:	**A Phase 1b/2, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 with Cobimetinib in Adult Participants with Relapsed/Refractory Solid Tumors and a Phase 1b Study of RMC-4630 with Osimertinib in Participants with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer**
Protocol Number:	RMC-4630-02
Compound Number:	RMC-4630
Study Phase:	Phase 1b/2
Short Title:	Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors and Study of RMC-4630 with Osimertinib in EGFR Positive NSCLC after Osimertinib Progression
Sponsor Name:	Revolution Medicines, Inc.
Legal Registered Address:	700 Saginaw Drive Redwood City, CA 94063
Regulatory Agency Identifying Number(s):	IND 138359
Version/Date:	V6.0 / 20 Nov 2020

SPONSOR SIGNATORY

02-Dec-2020

Date

Senior Vice President, Clinical Development

CRO Drug Safety Name and Contact Information:

Covance 24-hour US Call Center
Phone: 1 888 724 4908

Sponsor Medical Monitor Name and Contact Information:

Revolution Medicines, Inc.
Phone:

PROTOCOL SIGNATORY, PRINCIPAL INVESTIGATOR

Title:	**A Phase 1b/2, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 with Cobimetinib in Adult Participants with Relapsed/Refractory Solid Tumors and a Phase 1b Study of RMC-4630 with Osimertinib in Participants with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer**
Protocol No.:	RMC-4630-02
Version No. / Date:	V6.0 / 20 Nov 2020
Compound ID:	RMC-4630
Phase:	1b/2
Sponsor:	Revolution Medicines
Regulatory Agency Identifying No.:	IND 138359

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (Print)	**Principal Investigator's Signature**
Site Number	**Date (DD/MMM/YYYY)**

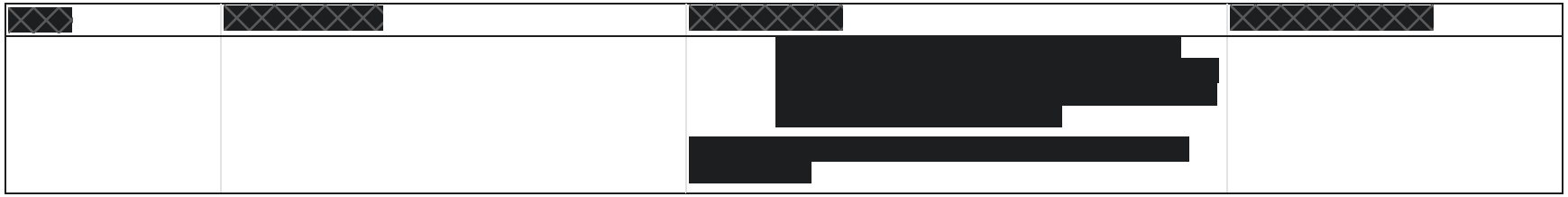
[redacted]

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]		
[redacted]	[redacted]	[redacted]
		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Section			



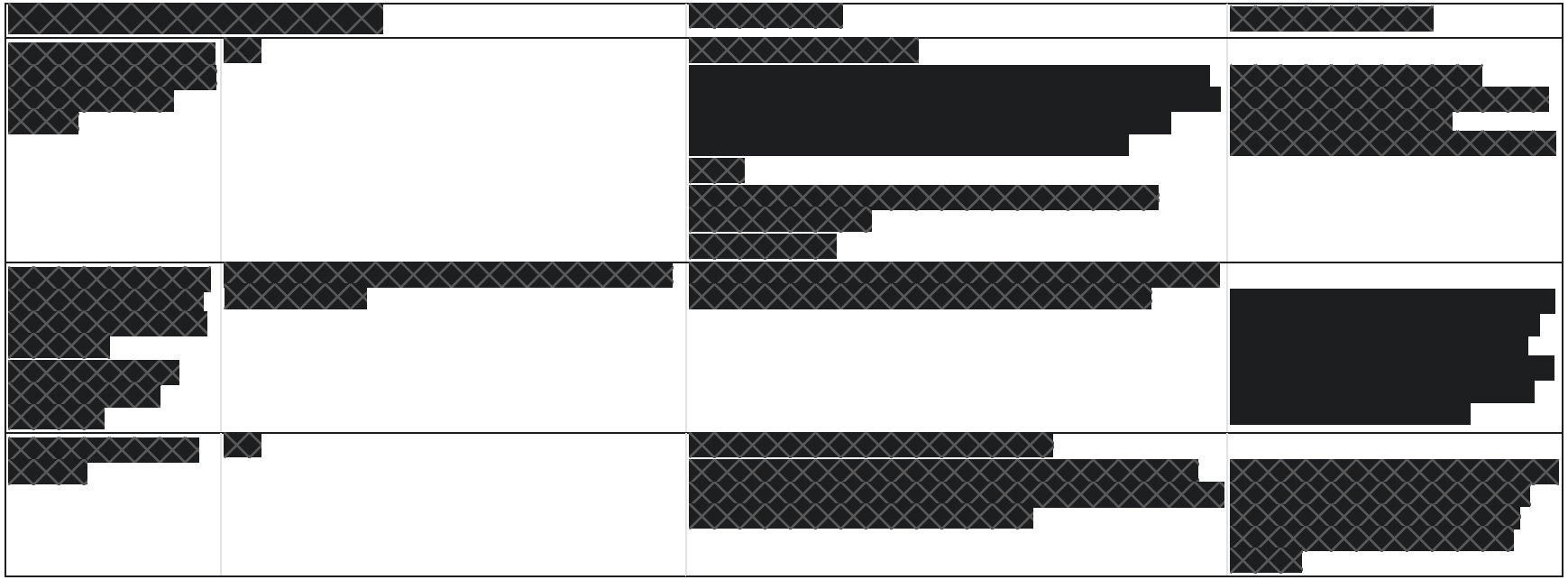


TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF TABLES

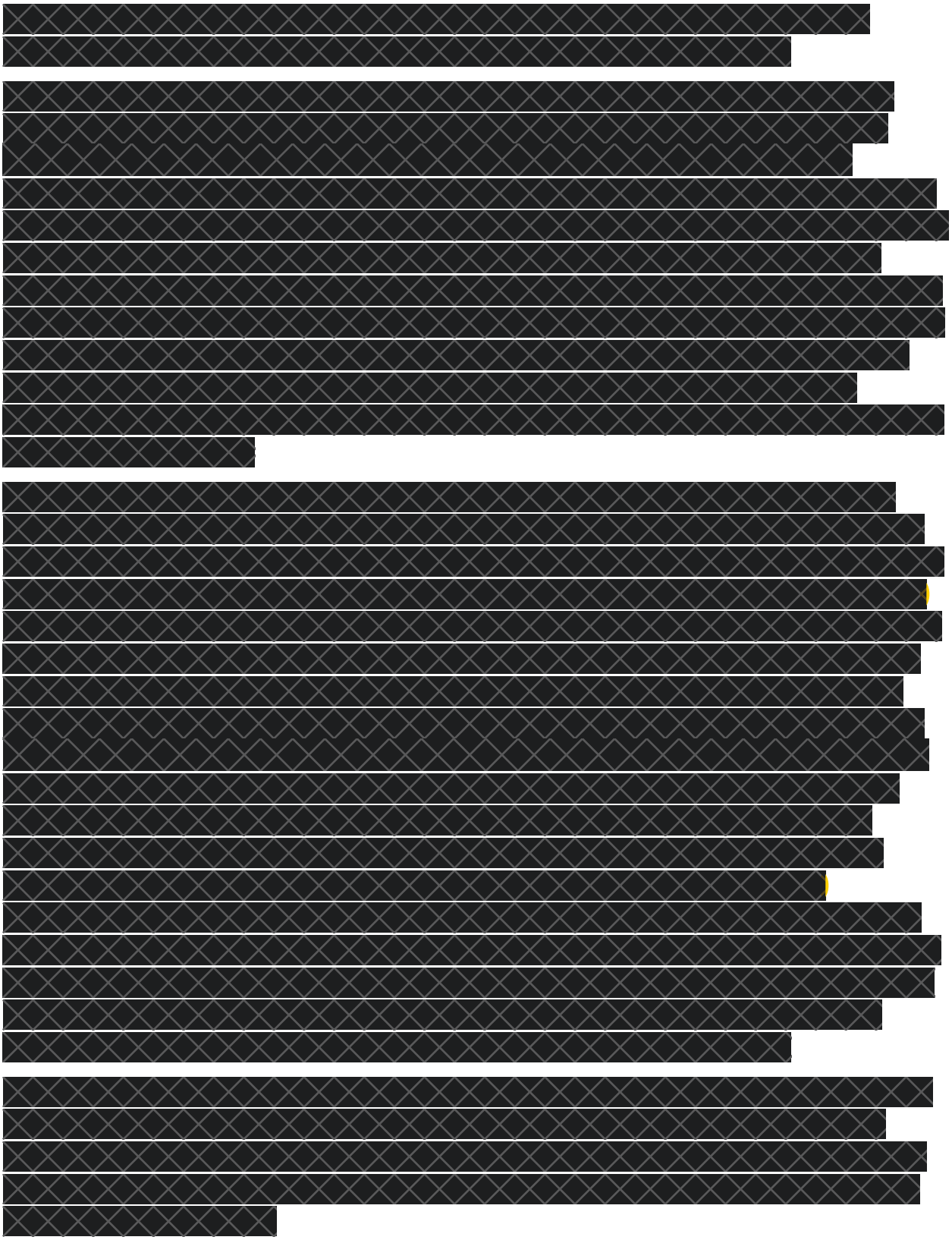
1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1b/2, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 with Cobimetinib in Adult Participants with Relapsed/Refractory Solid Tumors and a Phase 1b Study of RMC-4630 with Osimertinib in Participants with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Short Title: Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors and Study of RMC-4630 with Osimertinib in EGFR positive NSCLC after Osimertinib Progression

1.1.1. RMC-4630 and Cobimetinib (Study in US and ex-US Countries)



OBJECTIVES AND ENDPOINTS FOR RMC-4630 AND COBIMETINIB STUDY

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of the combination of RMC-4630 and cobimetinib in participants with relapsed/refractory solid tumors • To define the MTD and RP2D and schedules for the combination of RMC-4630 and cobimetinib in participants with relapsed/refractory solid tumors	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE v5 for the combination of RMC-4630 and cobimetinib • Incidence and nature of DLTs for the combination of RMC-4630 and cobimetinib
Secondary	
[redacted]	[redacted]
Tertiary/Exploratory	
• [redacted] •	[redacted]

Abbreviations: AE, adverse events; AUC_{0-t}, area under the curve from dosing time to time t; AUC_{inf}, area under the curve from dosing time to infinity; [redacted]; C_{max}, peak concentration; ctDNA, circulating tumor DNA; DCR, disease control rate; DLT, dose limiting toxicity; DOR, duration of response; MTD, maximum tolerated dose; [redacted], mutations in neurofibromin 1 predicted to result in loss of function; ORR, objective response rate; PFS, progression free survival; PK, pharmacokinetic(s); NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5; OS, overall survival; PFS, progression-free survival; PD, pharmacodynamic; RAS-MAPK, RAS-mitogen activated protein kinase; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, Version 1.1; RP2D, recommended phase 2 dose; SAE, serious adverse events; $t_{1/2}$, elimination half-life; T_{max}, time to achieve peak plasma concentration.

Overall Design

This study arm with RMC-4630 and cobimetinib will be conducted in US and ex-US countries. This arm includes two components: a Dose-Escalation Component and a Dose-Expansion Component. The overall schema is illustrated in Figure 1.

Prior to enrollment, all participants will undergo screening based on prior genomic testing using a clinically validated or qualified assay on either tumor tissue or circulating tumor DNA (ctDNA) samples. Questions regarding eligible mutations may be addressed to the Sponsor. Participants with at least one the following genotypes and histotypes will be enrolled

[redacted]

Archival tissue will be requested from all participants. For genomic reports based on clinically validated local tests and used for enrollment, retrospective analysis will be performed by a central lab on archival tissue for analysis and reporting purposes. A fresh biopsy will not be used to determine patient eligibility.

Dose-Escalation Component: This arm will begin with the Dose Escalation Component. The initial dose of RMC-4630 will be 80 mg administered orally (PO) twice weekly, D1 and D4, for 28 days of a 28-day cycle.

The starting dose of cobimetinib will be 20 mg PO administered daily (QD) on days 1-21 of a 28-day cycle (21/7 schedule). This dose is two dose levels below the approved dose of cobimetinib of 60 mg PO QD on the 21/7 schedule.

In addition to the planned dose levels, alternative dose schedules which allow D1, D2 dosing of either or both RMC-4630 and cobimetinib may be initiated and the starting dose will be based on the analysis of emerging safety and PK data. Therefore, RMC-4630 can be administered in either a D1, D4 or D1, D2 schedule. Whereas, cobimetinib can be administered in either once daily (21/7) or D1, D2 schedule. However, the single and monthly starting dose for cobimetinib will not exceed those already tested in clinical trials. The decision to trigger exploration of an alternative schedule will be made by the Dose-Escalation and Expansion Committee (also referred to as “Dose Committee”) after careful review of emerging toxicity profile of the combination.

Advancement to higher combination dose levels during the escalation phase will occur after an evaluation of safety and tolerability by the Dose Committee. The proposed continual reassessment method (CRM) will generate dose combination recommendations. The model estimates the probability of dose limiting toxicities (DLTs) in Cycle 1 (C1) at each candidate combination dose level to determine the dose combination to treat the next cohort. The MTD is selected as the combination associated with the highest posterior probability of DLT rating within the target interval of 25% - 35% and which have been used to treat at least 6 participants.

During escalation, a minimum of 3 participants on a combination dose level are required to be DLT evaluable to render a decision to proceed to the next dose level. A 4th participant, if available, may enroll onto the escalation dose before the first 3 participants have completed the DLT evaluation. DLT events for all participants at a given combination dose level will be entered into the CRM model and assessed by the Study Dose Committee. The first cycle (28 days) constitutes the DLT assessment period. Parallel Dose-Escalation Cohorts may be allowed.

Dose-Expansion Component: After the Dose-Escalation Component has ended and the RP2D is determined, a Dose-Expansion cohort of up to 90 participants (including those already enrolled at this dose in the Dose-Escalation and Expansion cohorts) will be enrolled at the RP2D. In this Dose-Expansion cohort, up to 15 participants in each of the 6 genotypic/histotypic cohorts will be enrolled.

Moreover, once the Dose-Escalation Component has reached a threshold of activity based on clinically meaningful reduction in tumor burden at a dose with acceptable toxicity, additional participants may possibly be enrolled at dose levels prior to the determination of RP2D. The Dose Committee will determine whether clinically meaningful reduction has been achieved (eg, ≥30% reduction in the sum of longest diameters of target lesions or a lesser diminution with a preponderance of clinical evidence of benefit). See ‘Dose-Escalation and Expansion Committee Charter’ for more information.

Expansion prior to RP2D may occur at more than one dose level. The current Dose-Expansion cohort will stop enrollment after the next higher dose combination in the Dose-Escalation Component is completed. At this point, the Dose-Expansion Cohort at the new higher level will open for enrollment if the dose is considered to have acceptable tolerability during the Dose-Escalation Component. Parallel Dose-Expansion cohorts may occur. A maximum of 12 participants (in both Dose-Escalation and Expansion cohorts) may enroll in each dose combination level. Once a dose level is expanded to include more slots, the sponsor may choose to reserve slots for genotypes/histotypes which are considered more likely to obtain clinical benefit based on the emerging clinical and/or biomarker data.

Duration of Therapy

Participants will be permitted to remain on study therapy until disease progression per RECIST v1.1, unacceptable toxicity, other criteria for withdrawal are met, or end of study (refer to Section 4.3), whichever comes first. Participants will return to the clinical site for an End of Treatment (EOT) visit within 30 days after last dose of study treatment.

1.1.2. RMC-4630 and Osimertinib (Study in US Only)

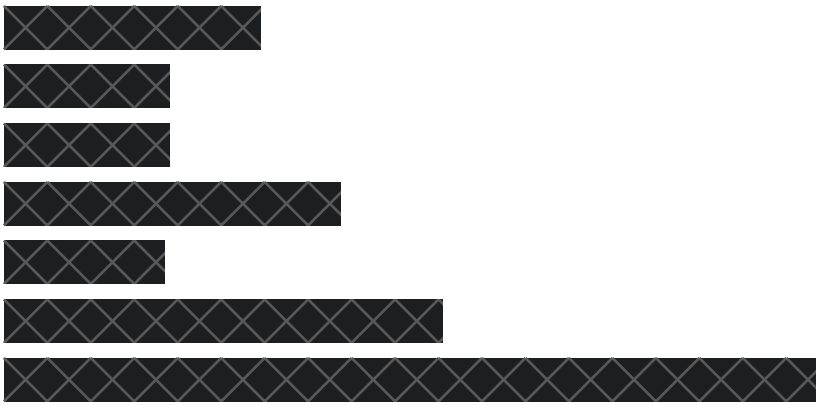
OBJECTIVES AND ENDPOINTS FOR RMC-4630 AND OSIMERTINIB STUDY

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of the combination of RMC-4630 and osimertinib in participants with EGFR mutation-positive NSCLC who have progressed on or after osimertinib	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE v5 for the combination of RMC-4630 and osimertinib
• To define the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D) and schedule for the combination of RMC-4630 and osimertinib in participants with EGFR mutation-positive NSCLC	• Incidence and nature of DLTs for the combination of RMC-4630 and osimertinib
Secondary	
[redacted]	[redacted]
[redacted]	[redacted]

Overall Design

This arm with RMC-4630 and osimertinib will be conducted ONLY in the US. It will include two components: a Dose-Escalation Component and a Dose-Expansion Component. The overall schema is illustrated in Figure 3.

Prior to enrollment into this arm, all participants will undergo screening to determine eligibility. Information regarding existing mutations at baseline will be collected using prior histological or ctDNA documentation for *EGFR* mutations. Sponsor will determine eligibility based on the presence of an *EGFR* mutation in the most recent genomic report (for the dose escalation component of the study). The following mutations/histologies will not be eligible to enroll:



Dose-Escalation Component: This arm will begin with the Dose Escalation Component. The starting dose of RMC-4630 will be 140 mg on D1 and D2. -The starting dose of osimertinib will be at the approved dose of 80 mg once daily. Alternative dose schedule for RMC-4630 including D1D4 dosing may be explored depending on emerging data from this study and other RMC-4630 studies. The decision for initial dose/schedule of RMC-4630 was made by the Dose Committee after careful evaluation of the safety data. Dose-Escalation scenario for RMC-4630 and osimertinib is shown in Figure 3.

The first cycle (eg, 28 days) constitutes the DLT assessment period. The first participant in the initial combination dose level will be observed for the first 7 days of dosing prior to dosing additional participants in this cohort. Following this 7-day observation period, additional participants may be enrolled in the cohort. In subsequent combination dose level cohorts, participants may be enrolled concurrently.

Dose-Expansion Component: After the Dose-Escalation Component has reached an MTD, the Dose committee will determine whether Dose-Expansion phase should be initiated and will determine RP2D which may or may not be the same as MTD but, would not exceed MTD. In Dose-Expansion, up to 6-18 participants may enroll depending on how many participants will enroll in the Dose-Escalation portion for a total of 24 participants in the RMC-4630 + osimertinib arm.

All participants in the Dose-Expansion phase will undergo screening to determine their eligibility. Participants will be eligible if the tumor harbors one or more of the genetic aberrations defined to be sensitive to SHP2 inhibition by the sponsor and does not harbor any co-occurring mutations which are not sensitive to SHP2 inhibition (Section 4.2, Appendix 9B).

Duration of Therapy

Participants will be permitted to remain on study therapy until disease progression per RECIST v1.1, unacceptable toxicity, other criteria for withdrawal are met, or end of study (refer to Section 4.3), whichever comes first. Participants will return to the clinical site for an End of Treatment (EOT) visit within 30 days after last dose of study treatment

Safety Committees

Two safety committees, the Dose-Escalation and Expansion Committee ("Dose Committee") composed of Sponsor representatives and investigators, and the Internal Safety Monitoring Committee (ISMC), consisting of internal Sponsor representatives including Medical Monitors (Sponsor and contract research organization [CRO]), Drug Safety Monitor, and biostatistician, will monitor the safety data from RMC-4630 program. The Dose Committee is study-specific while the ISMC is RMC-4630 program-specific. Details regarding membership and roles and responsibilities will be provided in the respective committee charters.

For both arms in this study, the Dose Committee will be responsible for evaluating the safety data during the DLT period and provide decisions regarding the actual dose escalation level based on safety data and any other relevant available information. The RP2D will be determined by the Sponsor based on the totality of the information available at all dose levels and should not exceed the MTD. Finally, the Dose Committee will determine whether the Dose Expansion Component may commence at the completion of a given Dose Escalation Cohort.

The ISMC will conduct regular safety data reviews as well as ad hoc emergent safety data review for all participants during the course of the trial.

1.2. Schemas

Figure 1 Phase 1b/2 RMC-4630 and Cobimetinib Study Schema

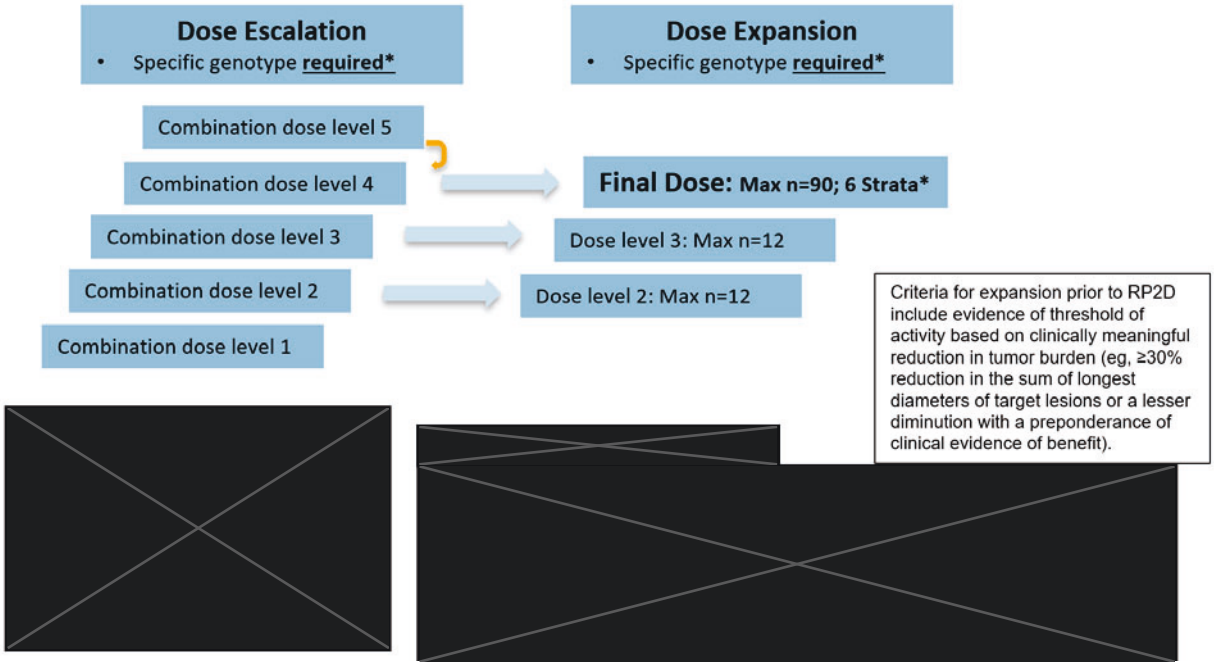


Figure 2 Dose Escalation Scenarios for RMC-4630 (D1, D4) and Cobimetinib (21/7)

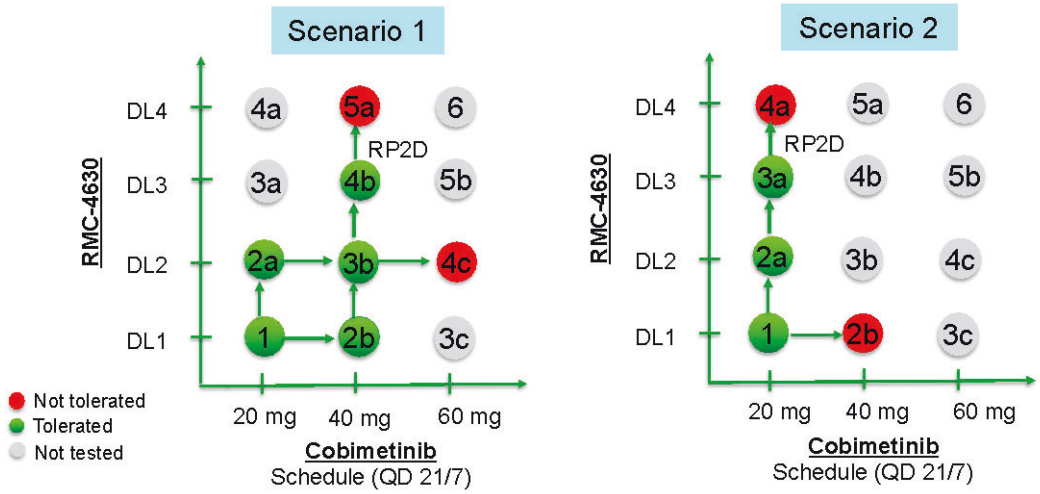


Illustration of two possible dose escalation scenarios (Figure 2). Other scenarios are possible but not shown. Beginning at combination dose level 1, participants are enrolled in a series of cohorts with each cohort having a minimum of 3 participants. The dose level of the next cohort

will be recommended from the Bayesian model; however, the actual dose selected will be determined by the Dose Committee based on evaluation of DLTs, the CRM model recommendations, and other available relevant information. Scenario 1 is one possible scenario and is used to estimate the sample size in Table 1. The designations “a”, “b”, and “c” are used to demonstrate different cohorts. Enrollment into cohorts 2a and 2b, may occur simultaneously, as may cohorts 4b and 4c. Escalation to next dose level will only occur after DLT evaluation of one or both parallel cohorts (eg, escalation to level 3 will only occur after DLT evaluation for both 2a and 2b). An alternative dose escalation path is represented in Scenario 2. If dosing on D1, D2 is triggered for either or both RMC-4630 and cobimetinib, the dose escalation scenarios will remain the same.

Number of Participants: Table 1 illustrates sample size estimation based on “Scenario 1” depicted in Figure 2. The study is expected to enroll approximately 144 participants in RMC-4630 and cobimetinib arm of the study.

Table 1 Sample Size Estimation

Figure 3 RMC-4630 and Osimertinib Study Schema (Study in US only)

Figure 4 Dose Escalation Scenario for RMC-4630 and Osimertinib

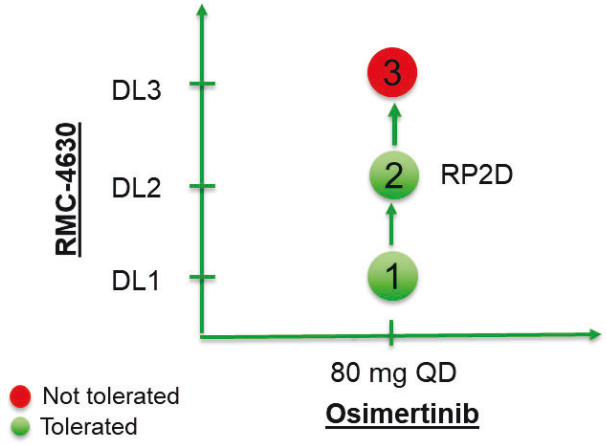
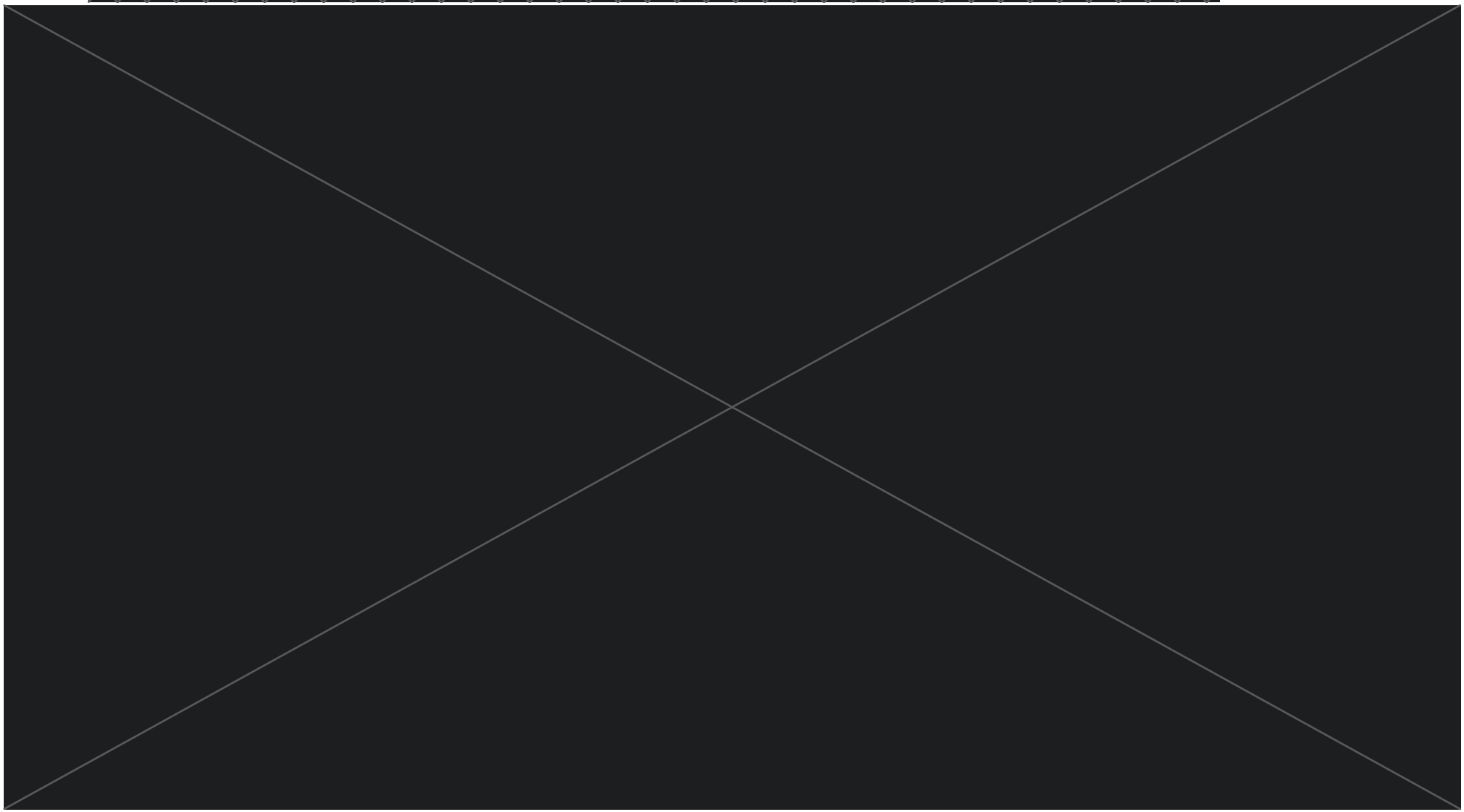


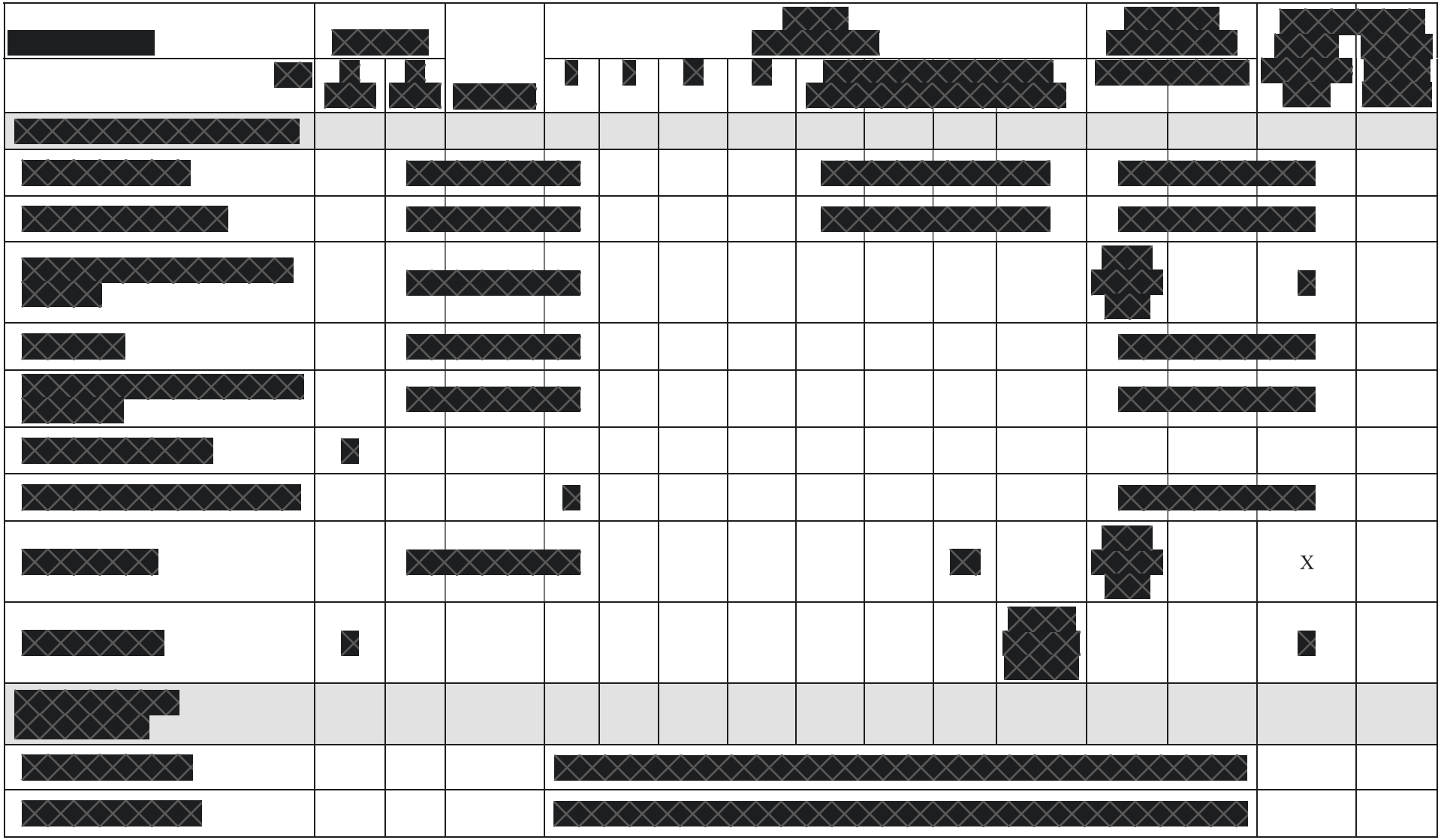
Illustration of possible dose escalation scenario (Figure 4). Beginning at combination dose level 1, participants are enrolled in a series of cohorts with each cohort having a minimum of 3 participants. The dose level of the next cohort has been pre-specified in the protocol; however, the actual dose selected will be determined by the Dose-Escalation Committee based on evaluation of DLTs and other available relevant information. The designations "1", "2", and "3" are used to demonstrate different escalation cohorts at different dose levels. Enrollment into cohorts will be sequential. Escalation to next dose level will only occur after DLT evaluation.

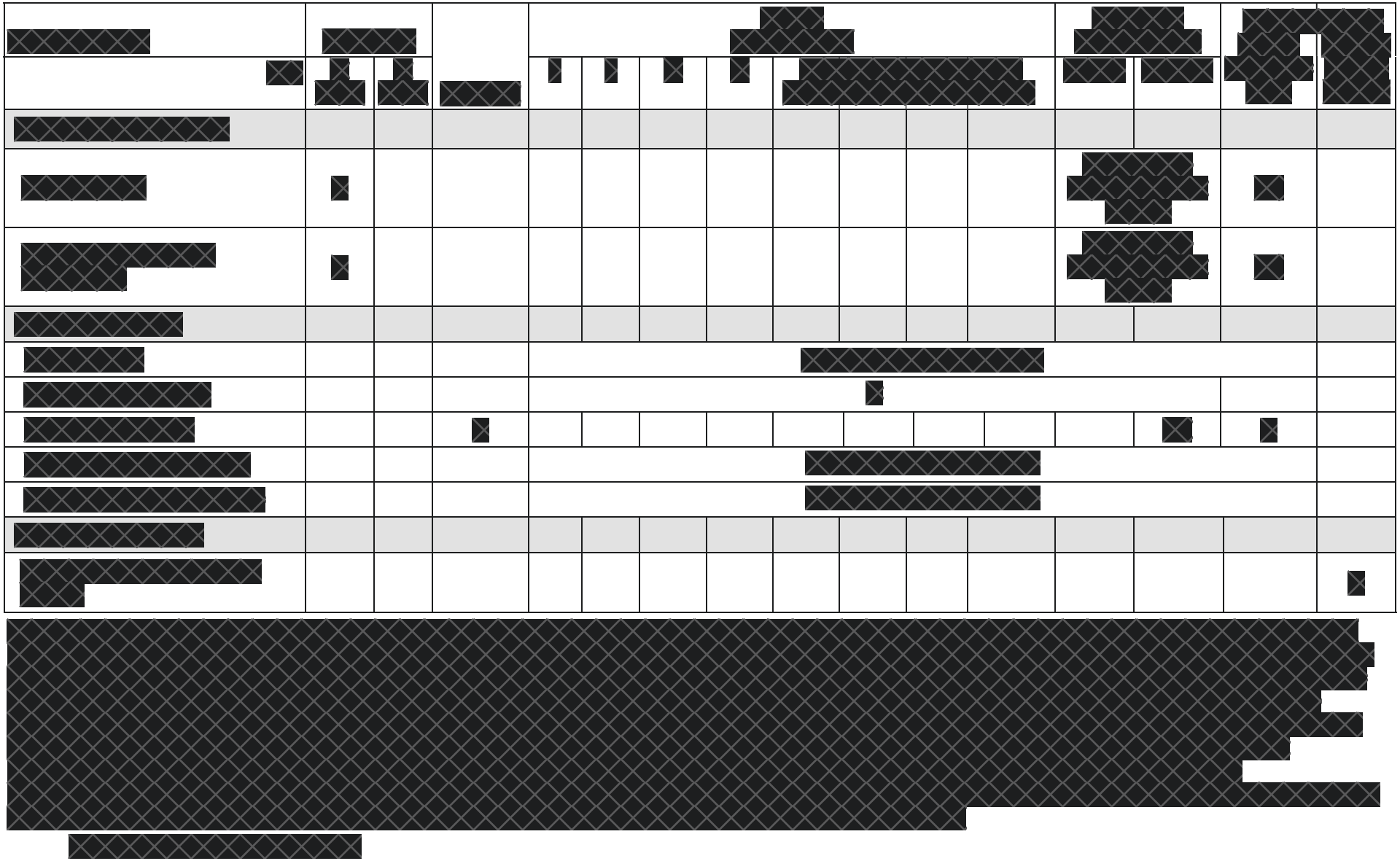
1.3. Schedule of Activities (SoA)

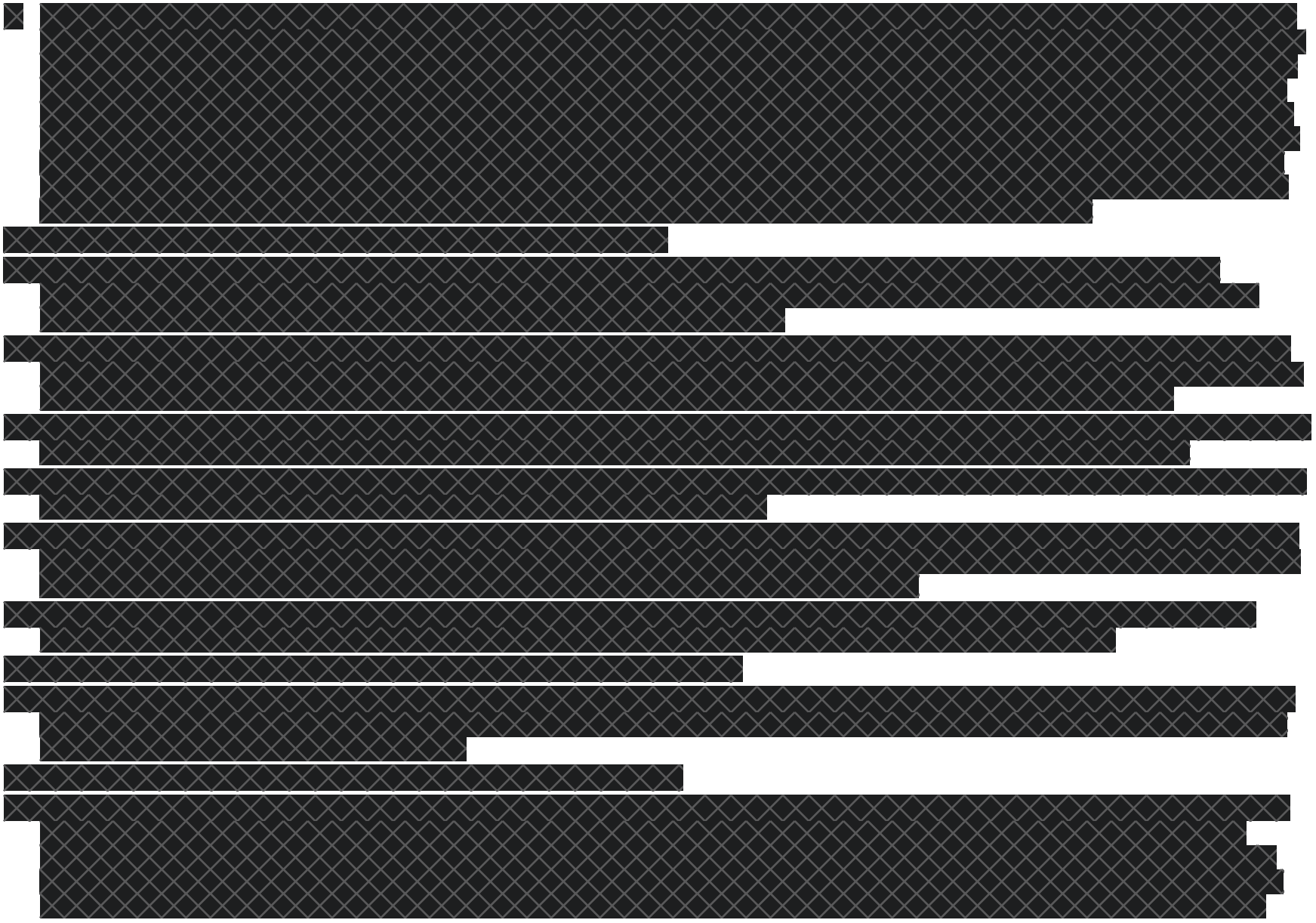
1.3.1. [redacted]

[redacted]



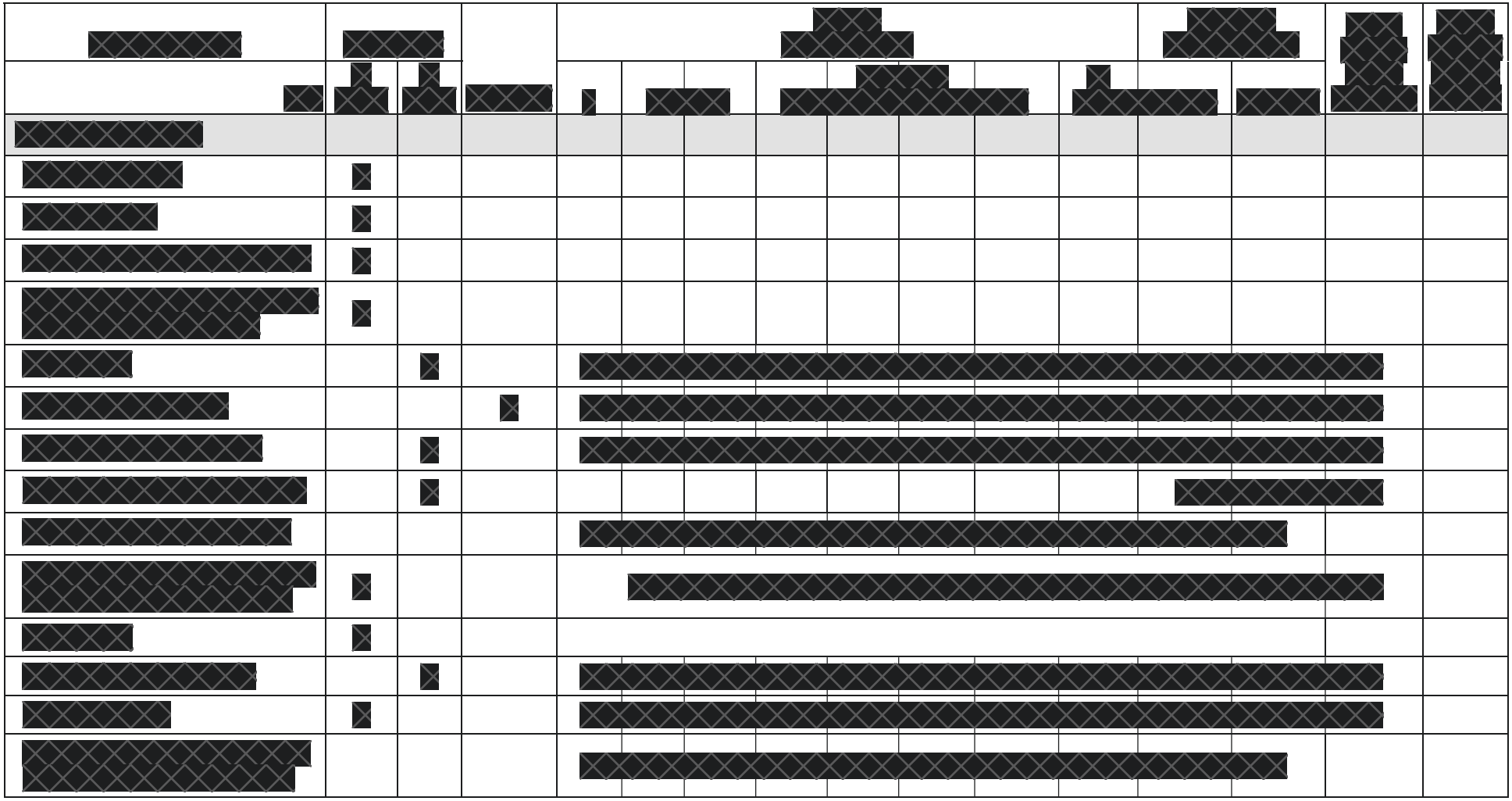

X

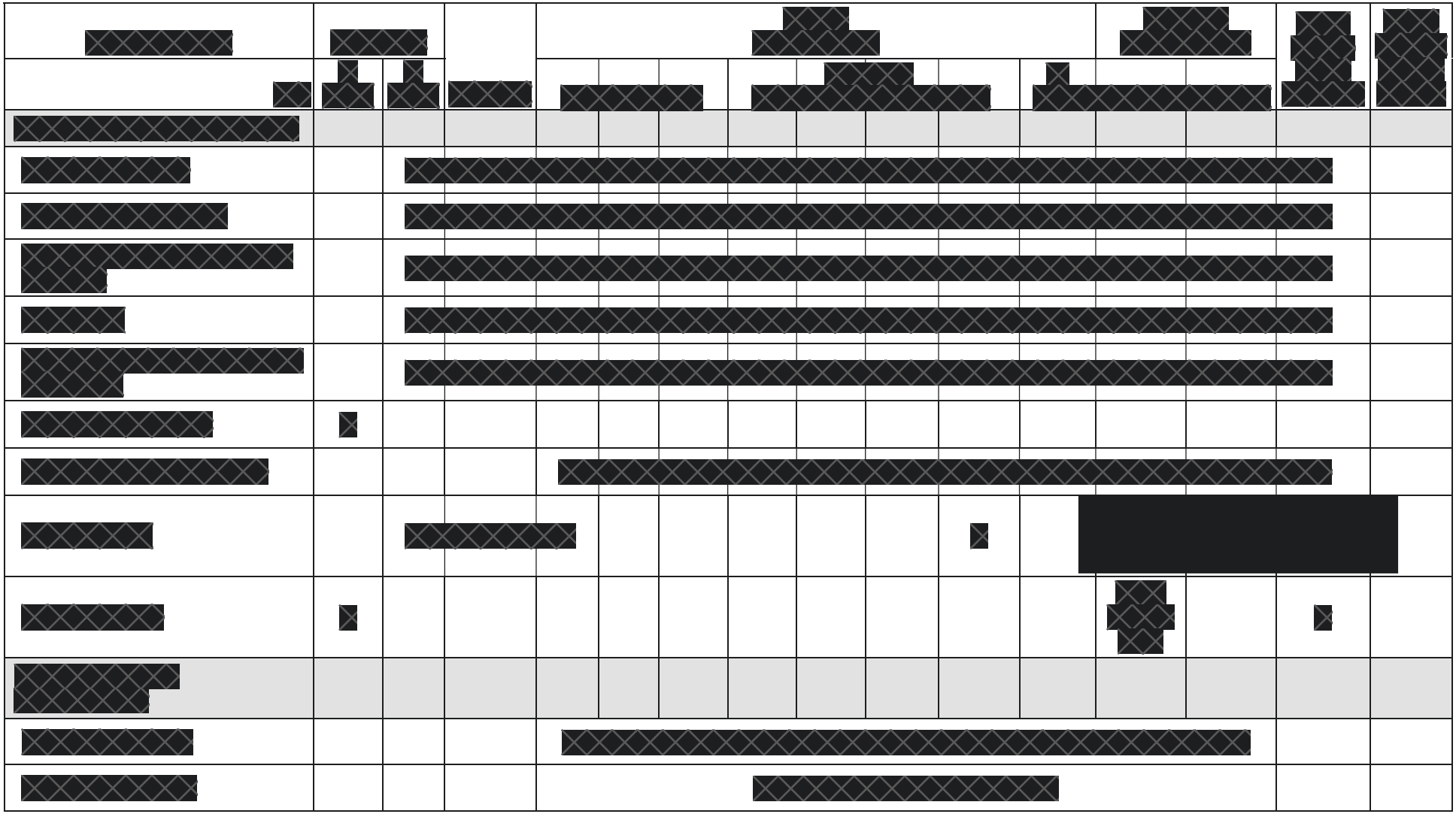


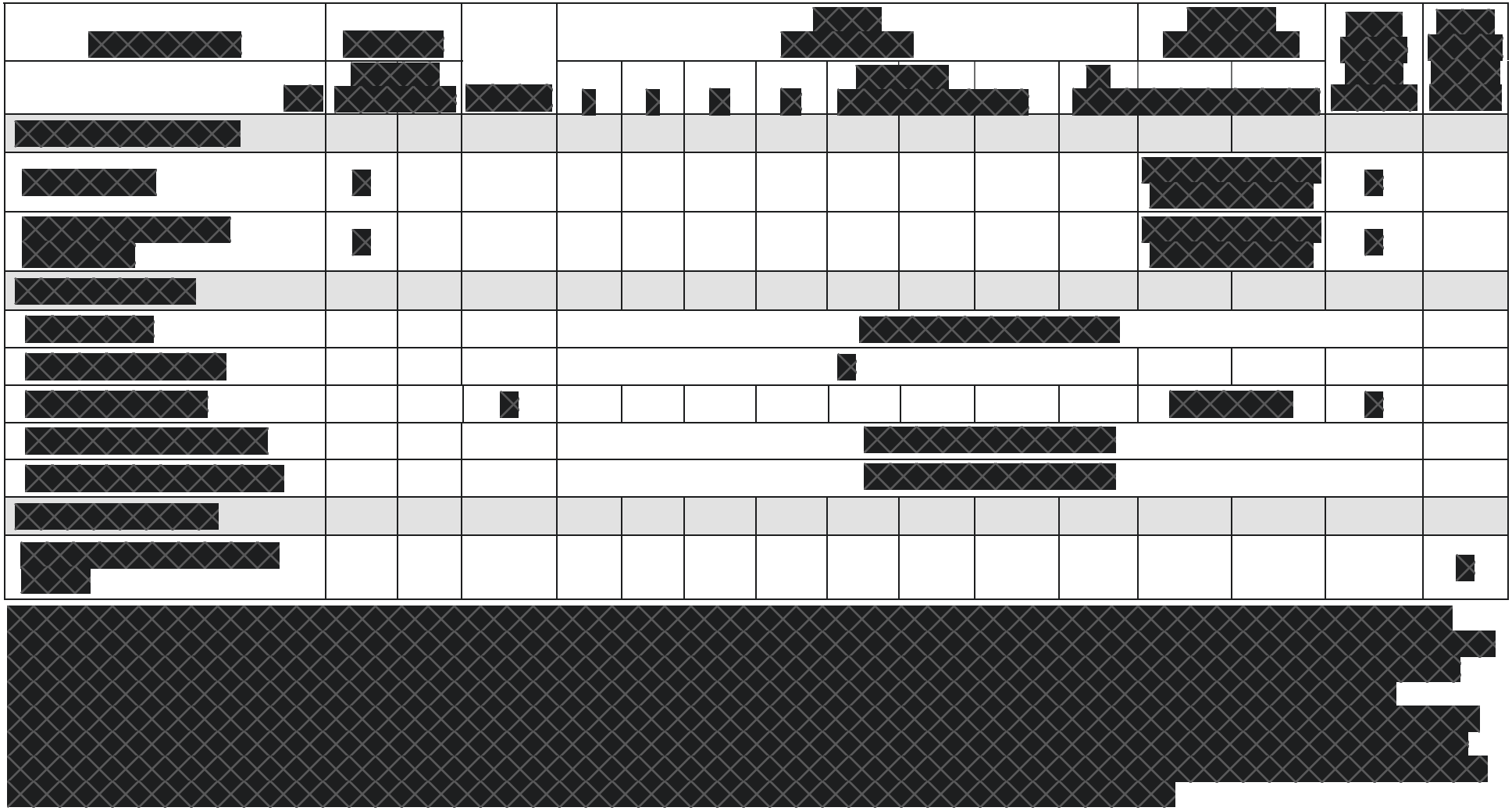


1.3.2. [redacted]

[redacted]







See Footnotes on the following page.

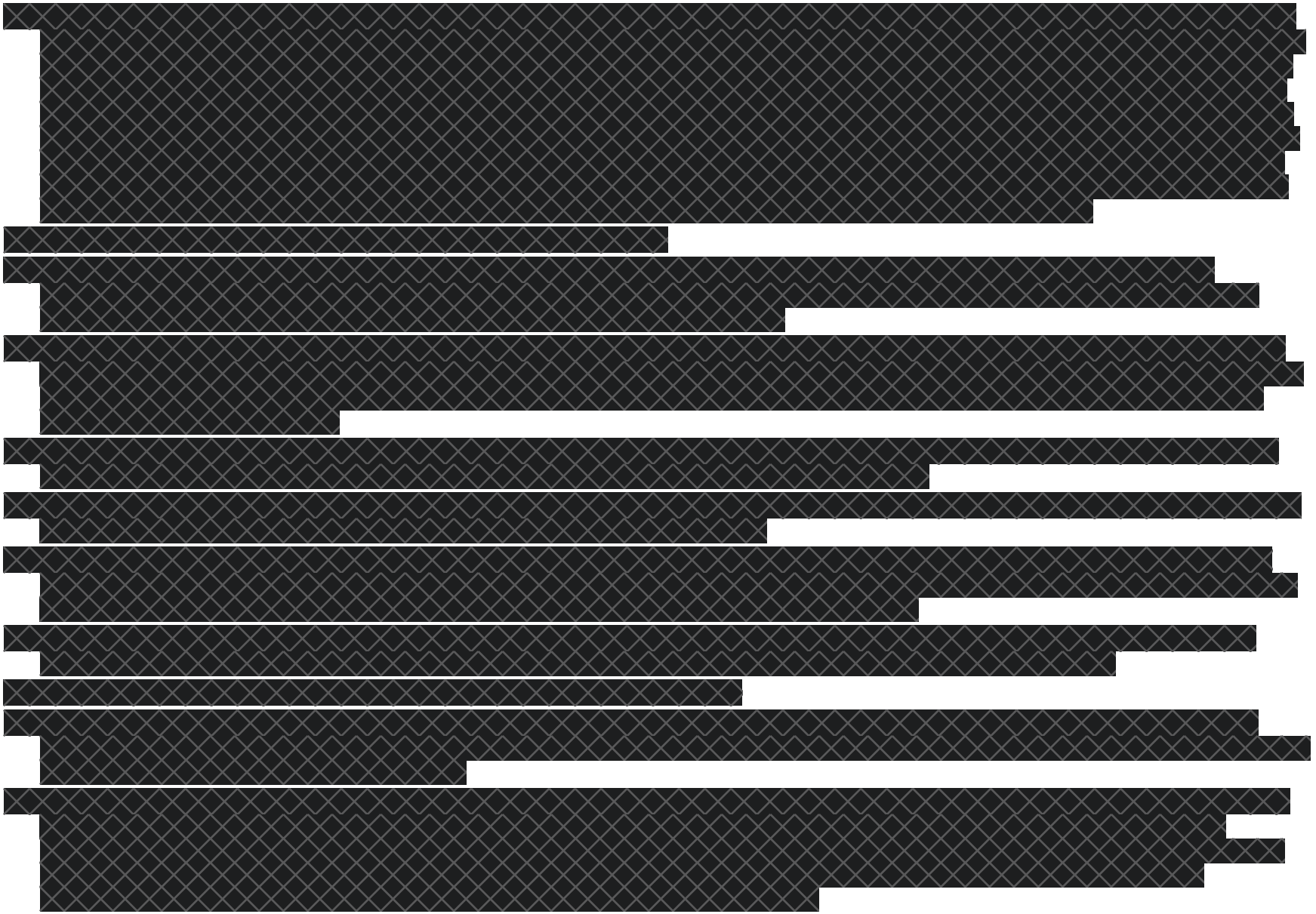
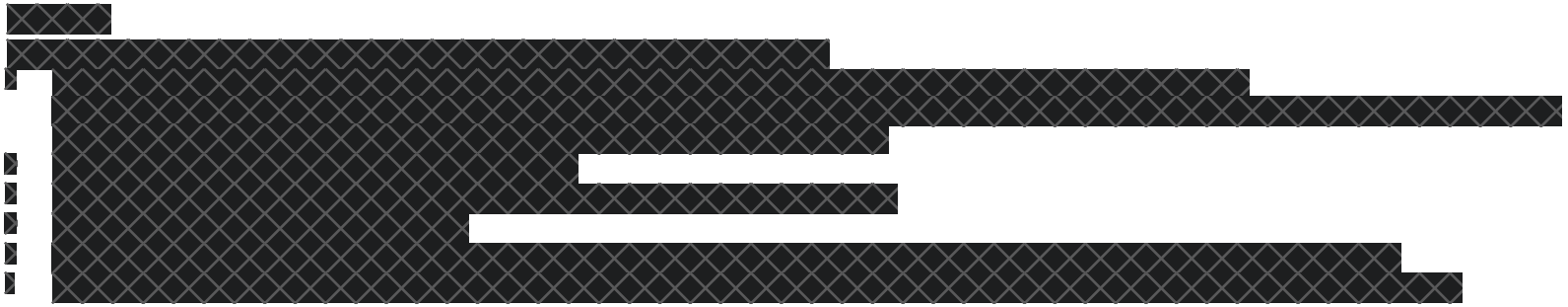


Table 2

See Footnotes on the following page.



2. INTRODUCTION

RMC-4630 is a potent, selective, and orally bioavailable SHP2 allosteric inhibitor that is being developed for patients with tumors harboring certain activating genotypic aberrations in the RAS/MAPK pathway.

Cobimetinib is an orally bioavailable, small molecule inhibitor of MEK1/2 which is approved in combination with vemurafenib, a BRAF inhibitor, for the treatment of advanced BRAFV600E/K mutated melanoma.

Osimertinib is an oral kinase inhibitor of the epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion), and is indicated for first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by a United States Food and Drug (US FDA)-approved test. It is also indicated for patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

2.1. Study Rationale

2.1.1. RMC-4630 and Cobimetinib Combination

[redacted]

2.1.2. RMC-4630 and Osimertinib Combination (Study in US Only)

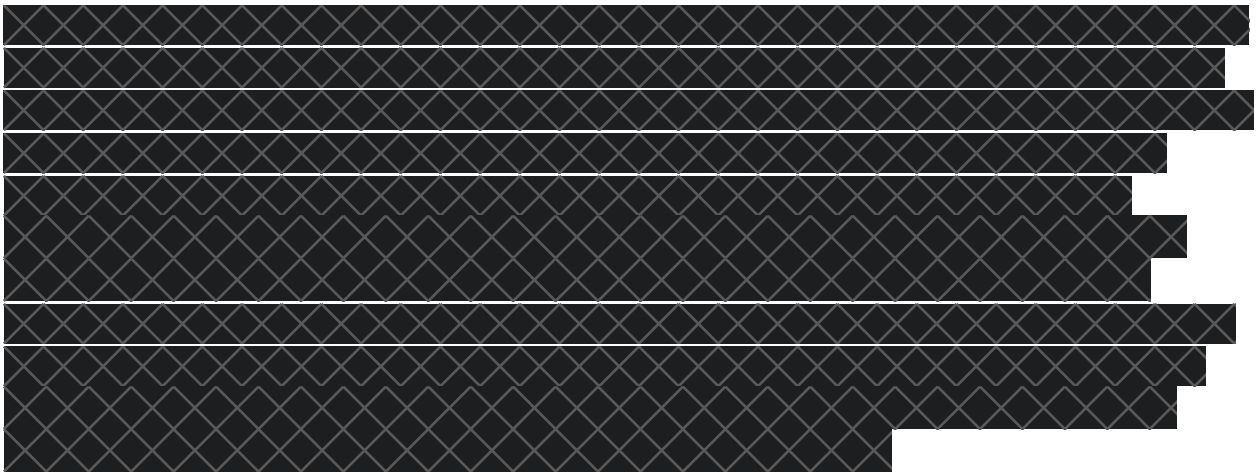
[redacted]

[redacted]

2.2. Background

2.2.1. RMC-4630 and Cobimetinib Combination

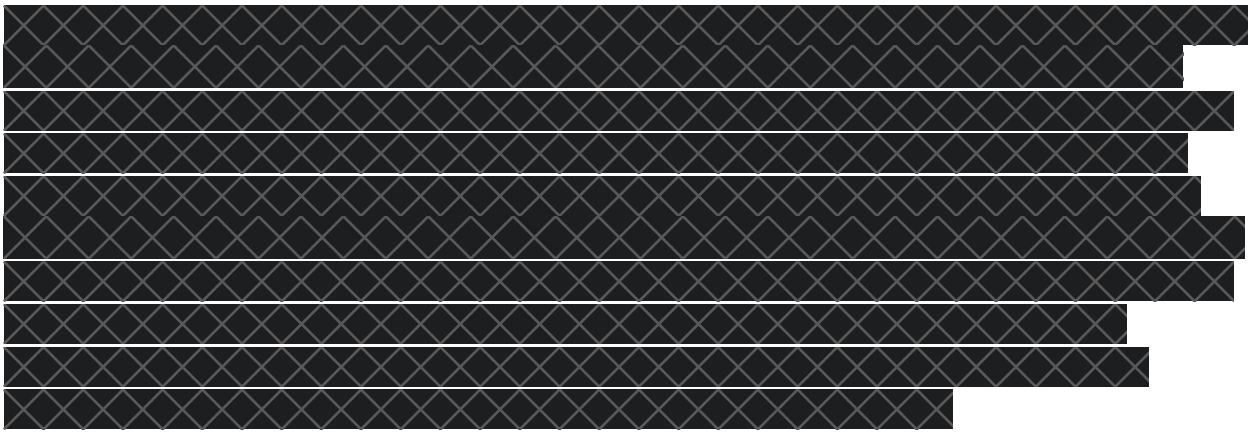
SHP2 is a non-receptor protein tyrosine phosphatase and scaffold protein that functions downstream of multiple receptor tyrosine kinases (RTKs), integrating cell surface growth factor signals to promote RAS activation (Figure 5). RMC-4630 was designed as a potent and selective SHP2 allosteric inhibitor that suppresses RAS activation and the proliferation in cancers that, distinct from those dependent on oncogenic RTKs, are driven by nucleotide cycling oncogenic point mutations [redacted]



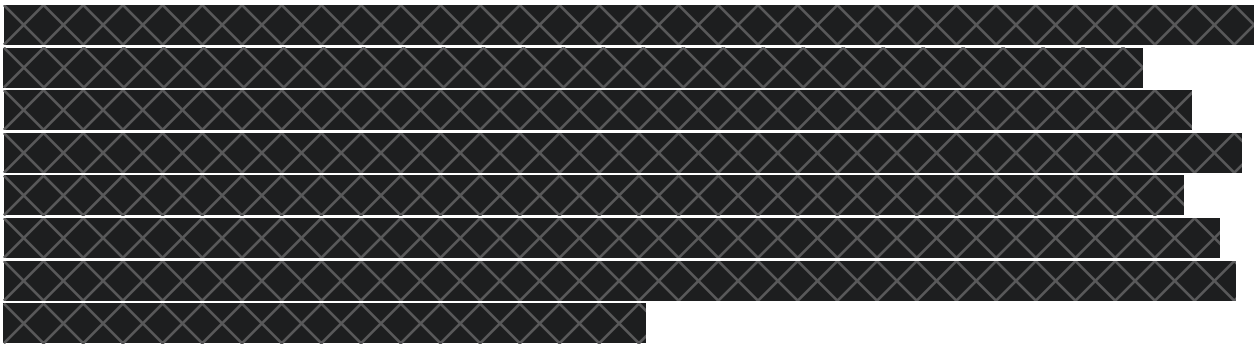
Unfortunately, in most models, tumor cytostasis was followed by regrowth of tumors, reminiscent of patterns observed with BRAF and MEK inhibitors, where initial response to single agents is followed by tumor resurgence and resistance on treatment (Fedele 2018). In the NCI-H358 *KRAS*^{G12C} model of NSCLC, examination of the pharmacokinetic/ pharmacodynamic (PK/PD) relationship for SHP2 inhibition demonstrated that maximal concentrations of SHP2 inhibitor achieved ~75% inhibition (relative to control) of phospho-ERK1/2 (pERK), a downstream indicator of oncogenic flux via RAS (RevMed data on file). In total, these results support the hypothesis that pharmacologic inhibition of a single node within the RAS-MAPK pathway results in incomplete pathway inhibition and tumor persistence.

Consequently, the combination of MEK inhibitors and a SHP2 allosteric inhibitor was evaluated as a strategy to attenuate this feedback hyperactivation, restore efficacy, and forestall resistance in CDX and PDX models with oncogenic RAS-MAPK pathway mutations (RevMed data on

file). Concurrent targeting of SHP2 and the downstream MEK confers greater anti-tumor efficacy and was observed in models that were heretofore responsive to SHP2 inhibitor monotherapy. More consistent and greater tumor regressions with combination therapy were observed than can be attained with single agents that target these nodes within the RAS-MAPK pathway. Similarly, the combination of SHP2 and MEK inhibition enhance the sensitivity of *KRAS*-amplified cancer models both in vitro and in vivo (Wong 2018).



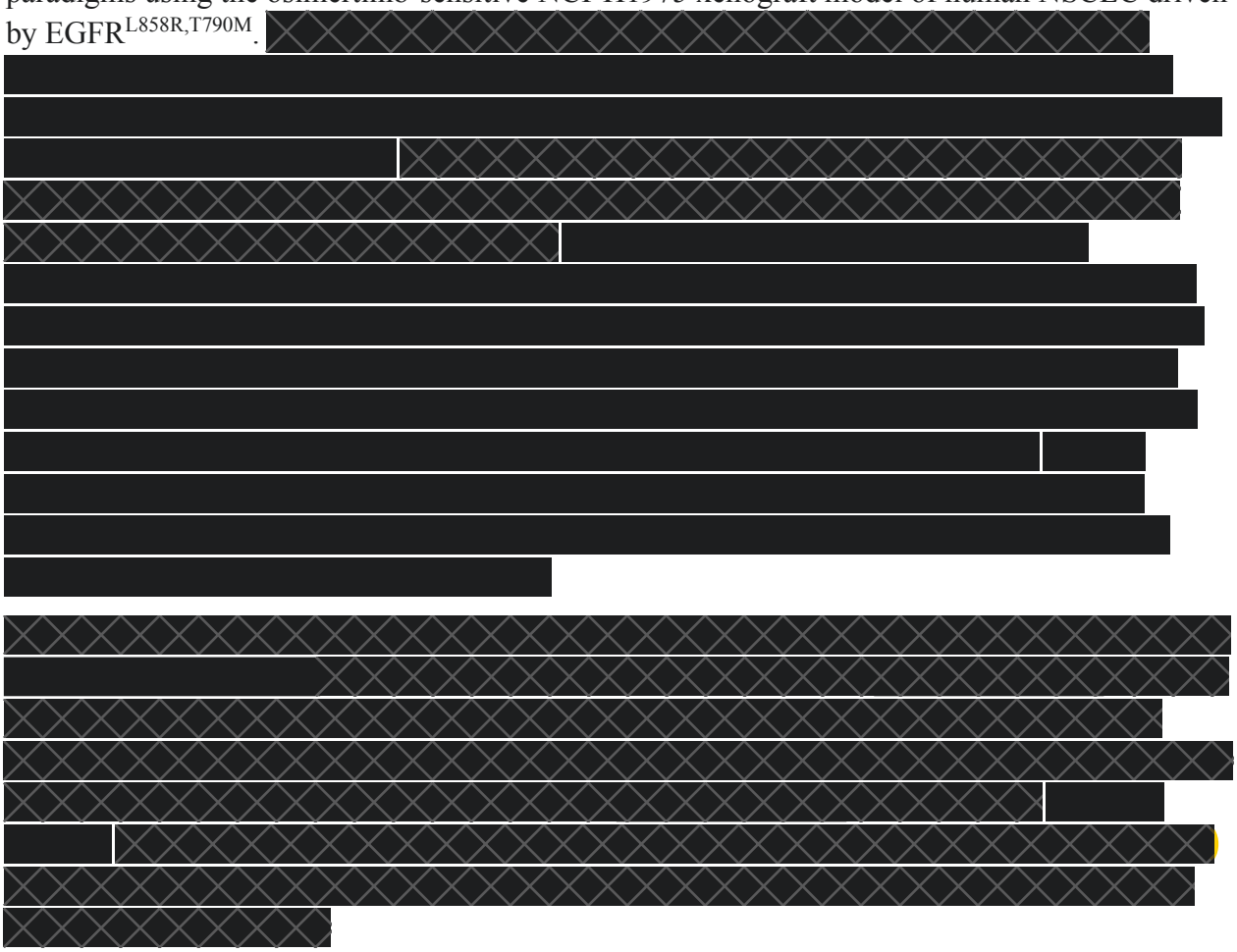
The combination regimen achieved greater duration of tumor pERK inhibition, reflecting either SHP2 inhibitor-mediated attenuation of RTK-driven feedback mechanisms and/or stronger pathway suppression per se. As a consequence, the combinatorial effects on inhibition of tumor cell proliferation as well as induction of apoptosis were observed. Moreover, recent publications have highlighted the potential for the combination of SHP2 inhibition with MEK inhibition in RAS mutant cancer cell lines that are insensitive to SHP2 or MEK inhibitor monotherapy (RevMed data on file; Fedele 2018, Mainardi 2018, Ruess 2018).



In summary, the findings reveal potential therapeutic approaches that use a potent SHP2 inhibitor in combination with another in-pathway inhibitor to counteract the evolution of resistance in tumors harboring alterations in the RAS-MAPK pathway. Additionally, the combination of SHP2 inhibition with MEK inhibition has the potential to provide therapeutic benefit in tumors driven by oncogenic mutations insensitive to either agent alone.

2.2.2. RMC-4630 and Osimertinib Combination (Study in US only)

The combination of RMC-4630 with osimertinib was examined under two different experimental paradigms using the osimertinib-sensitive NCI-H1975 xenograft model of human NSCLC driven by $EGFR^{L858R,T790M}$.



Resistance to osimertinib treatment is often driven by reactivation of RAS-MAPK signaling through myriad mechanisms including alternate RTK-mediated bypass (Oxnard 2018) such as amplification of MET. SHP2 functions as a convergent node downstream of multiple RTKs to regulate RAS activation. SHP2 inhibition is predicted to be effective in a variety of situations wherein RTK bypass drives resistance to RAS-MAPK pathway inhibitors (Dardaei 2018, Lu 2019).

In summary, these findings reveal potential therapeutic approaches that use a potent SHP2 inhibitor in combination with a third-generation EGFR inhibitor, osimertinib, to either counteract

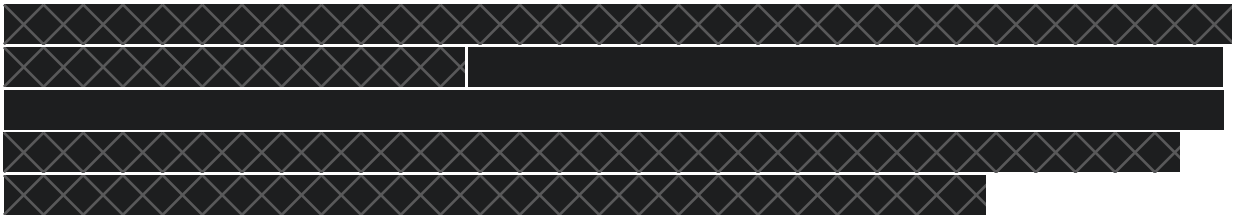
the evolution of resistance in tumors harboring EGFR alterations, or to re-sensitize osimertinib-resistant tumors wherein RTK bypass mechanisms drive reactivation of RAS-MAPK signaling.

2.3. Benefit/Risk Assessment

RMC-4630 and Cobimetinib Combination

Most patients with mutations/rearrangements that confer hyperactivation of the RAS-MAPK pathway have a poor prognosis. The combination of SHP2 inhibition together with MEK1/2 inhibition provides a potentially novel targeted treatment for these patients with relapsed or refractory solid tumors harboring mutations resulting in hyperactivation of the RAS-MAPK pathway.

RMC-4630 is currently being administered to humans in a phase 1 dose-escalation and dose-expansion monotherapy study, Protocol RMC-4630-01, (https://clinicaltrials.gov; NCT03634982) evaluating its safety, tolerability, MTD, and RP2D, PK, and PD profiles. More detailed information about the expected benefits and risks and reasonably expected adverse events of RMC-4630 based on clinical and pre-clinical data and class of drugs may be found in the RMC-4630 IB.



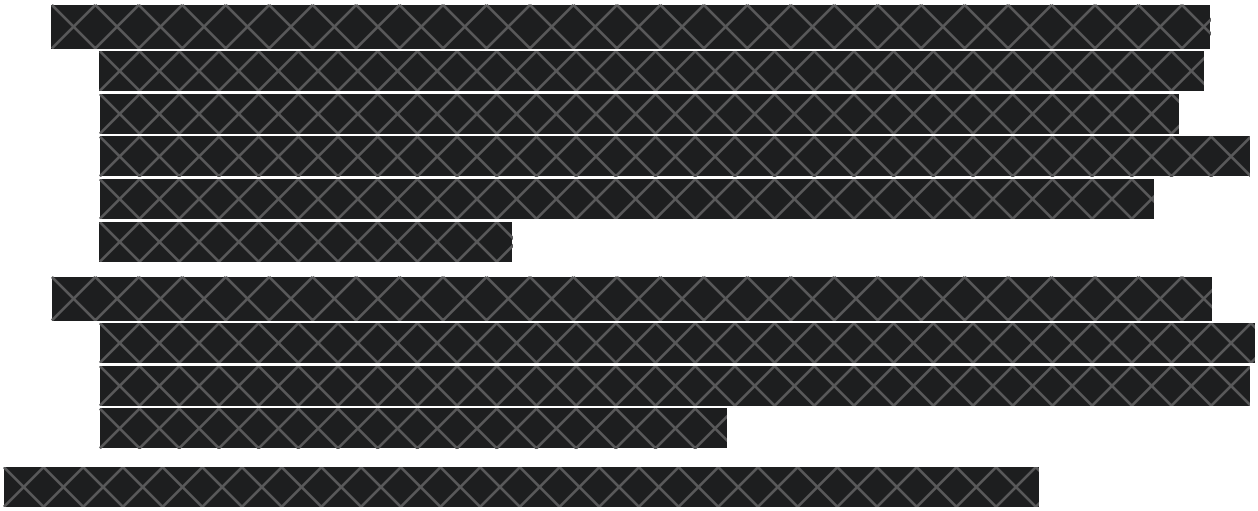
RMC-4630 and Osimertinib Combination (Study in US Only)

Osimertinib has been administered in clinical trials and is approved as first line treatment of patients with metastatic NSCLC whose tumors have an EGFR exon 19 deletion or exon 21 L858R mutation, as detected by an FDA approved test. Per National Comprehensive Cancer Network (NCCN) guidelines, osimertinib can be continued in patients post progression if benefit outweighs the risk. More detailed information regarding known benefits, risks, and expected adverse events of osimertinib may be found in the Tagrisso United States package insert.

Most patients that are currently receiving treatment with osimertinib will progress due to a resistance mechanism which may or may not be detected by a tissue biopsy or ctDNA. Some of these patients will continue to receive treatment with osimertinib as a single agent (NCCN guidelines). In patients that have progressed on or after osimertinib or an osimertinib containing regimen, the combination of a SHP2 inhibitor with osimertinib may reverse osimertinib resistance mechanism(s) and prolong its benefit. Osimertinib may be the most recent prior therapy before starting combination treatment with SHP2 inhibitor. Alternatively, patients with intervening therapies (such as chemotherapy) after osimertinib progression may be allowed.

[redacted]

[redacted]



2.3.1.2. Potential Risks of Cobimetinib

In a Phase 1a study, two dosing schedules of cobimetinib monotherapy were assessed: 21 days of a 28 cycle (21/7) and 14 days of a 28 day schedule (14/14) (MEK 4592g). All patients in this study experienced an adverse event (AE). The most frequent AEs were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea, vomiting (33.9% each), and edema peripheral (28.7%). Other events that occurred in ≥10% of patients included anemia, abdominal pain, constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased aspartate aminotransferase (AST), dermatitis acneiform, pruritus, and dry skin. Four DLTs with a 21/7 dosing schedule were observed in this monotherapy trial. At the 40 mg 21/7 dose level, a DLT of Grade 4 hepatic encephalopathy and Grade 3 elevated ammonia. At the 60 mg 21/7 dose level, a DLT of Grade 3 rash was reported. At the 80 mg 21/7 dose level, two DLTs were reported: 1 patient with Grade 3 diarrhea and 1 patient with Grade 3 rash (cobimetinib IB).

The best described combination studies of cobimetinib involve concurrent administration with vemurafenib in metastatic melanoma. In the Phase 1b dose-escalation study, the most common adverse events were diarrhea (64%), non-acneiform rash (60%), liver enzyme abnormalities (50%), fatigue (48%), nausea (45%), and photosensitivity (40%). Most adverse events were mild-to-moderate in severity. The most common Grade 3 or 4 adverse events were cutaneous squamous-cell carcinoma (9%; all Grade 3), raised alkaline phosphatase (ALP) (9%), and anemia (7%) (Ribas 2014). In the subsequent confirmatory phase 3 trial of cobimetinib and vemurafenib vs. vemurafenib in melanoma patients, the combination of vemurafenib and cobimetinib was associated with a higher frequency of certain events than the single-agent vemurafenib therapy, including central serous retinopathy, gastrointestinal events (eg, diarrhea, nausea, or vomiting), photosensitivity, elevated aminotransferase levels, and an increased creatine phosphokinase (CPK) level; the majority (>50%) of these individual events were Grade 1 or 2. Equivalent rates of Grade 3 events (49%) in the two study groups and substantially fewer Grade 4 events (9% control vs. 13% combination), with close to half of these in the experimental group being

due to laboratory abnormalities (elevated AST, alanine aminotransferase [ALT], and CPK levels) but without symptoms. An elevated CPK level, a known class effect of MEK blockade, was the single most common Grade 4 event (4%) with the combination therapy, although the majority of events related to CPK (66%) were Grade 1 or 2 (Larkin 2014).

In total, the most common AEs of cobimetinib (≥20%) are diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting. The most common (≥5%) Grade 3-4 laboratory abnormalities are increased gamma-glutamyl transferase (GGT), increased CPK, hypophosphatemia, increased ALT, lymphopenia, increased AST, increased ALP, hyponatremia. Moreover, serious risks of cobimetinib and vemurafenib administration include (Cobimetinib US Package Insert):

- **New primary cutaneous and non-cutaneous malignancies:** Cutaneous neoplasms and premalignant lesions including keratoacanthoma, basal cell carcinoma, cutaneous squamous cell carcinoma, and secondary melanoma occurred in combination therapy of vemurafenib plus cobimetinib. Non-cutaneous malignancies were reported in 0.8% of the vemurafenib and cobimetinib arm and 1.2% of the vemurafenib arm.
- **Hemorrhage including major hemorrhagic events**: The incidence of hemorrhage was higher in those receiving the combination of cobimetinib and vemurafenib therapy in comparison with those receiving vemurafenib (eg, Grade 3-4 hemorrhage 1.2% vs. 0.8%; all grades hemorrhage 13% vs. 7%). Cerebral, gastrointestinal, reproductive system hemorrhage, and hematuria were observed.
- **Cardiomyopathy:** Grade 2 or 3 decrease in left ventricular ejection fraction (LVEF) occurred in 26% of patients receiving cobimetinib with vemurafenib and 19% of patients receiving vemurafenib plus placebo. The median time to first onset of LVEF decrease was 4 months (range 23 days to 13 months) and median time to resolution of 3 months (range: 4 days to 12 months, among 62% of affected participants).
- **Severe dermatologic reactions**: Grade 3 to 4 rash, occurred in 16% of patients receiving cobimetinib with vemurafenib and in 17% of patients receiving vemurafenib plus placebo. The incidence of rash resulting in hospitalization was 3.2% in patients receiving cobimetinib with vemurafenib and 2.0% in patients receiving vemurafenib plus placebo. In patients receiving cobimetinib, the median time to onset of Grade 3 or 4 rash events was 11 days (range: 3 days to 2.8 months) and 95% experienced complete resolution with the median time to resolution of 21 days (range 4 days to 17 months).
- **Serous retinopathy and retinal vein occlusion**: With prospective serial ocular examinations, 26% of patients receiving cobimetinib and vemurafenib demonstrated serious retinopathy. The majority of these events were reported as chorioretinopathy (13%) or retinal detachment (12%). The onset of serious retinopathy occurred between 2 days to 9 months and the duration was 1 day to 15 days. Retinal vein occlusion

occurred in one patient in each arm (cobimetinib plus vemurafenib and vemurafenib arms).

- **Hepatotoxicity:** The incidences of Grade 3 or 4 liver laboratory abnormalities among patients receiving cobimetinib with vemurafenib compared to patients receiving vemurafenib plus placebo were: 11% vs. 6% for ALT, 7% vs. 2.1% for AST, 1.6% vs. 1.2% for total bilirubin, and 7% vs. 3.3% for ALP. Concurrent increase in ALT > 3 × upper limit of normal (ULN) and bilirubin > 2 × ULN in the absence of significant ALP > 2 × ULN occurred in 1 patient receiving cobimetinib and vemurafenib and no patients receiving vemurafenib.
- **Rhabdomyolysis and increased creatine phosphokinase**: Grade 3 or 4 CPK elevations, including asymptomatic elevations over baseline, occurred in 12% of patients receiving cobimetinib with vemurafenib and 0.4% of patients receiving vemurafenib. The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 12 days to 11 months) in patients receiving cobimetinib with vemurafenib; the median time to complete resolution was 15 days (range: 9 days to 11 months). Elevation of blood CPK increase of more than 10 times the baseline value with a concurrent increase in blood creatinine of 1.5 times or greater compared to baseline occurred in 3.6% of patients receiving cobimetinib with vemurafenib and in 0.4% of patients receiving vemurafenib. Rhabdomyolysis has been observed in patients receiving cobimetinib.
- **Severe photosensitivity**: Events of photosensitivity have been reported in 47% of participants receiving cobimetinib when administered with vemurafenib, although primarily reported as non-serious and low-grade events. 4% of patients experienced Grade ≥3 photosensitivity events. Median time to onset of photosensitivity of any grade was 2 months and the median duration was 3 months in patients receiving cobimetinib plus vemurafenib. The majority (63%) of patients experiencing photosensitivity had resolution of this symptom.
- **Embryo fetal toxicity**: Based on its mechanism of action and findings from animal reproduction studies, cobimetinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses resulting in exposures (AUCs) that were 0.9 to 1.4X those observed in humans at the recommended dose of 60 mg.

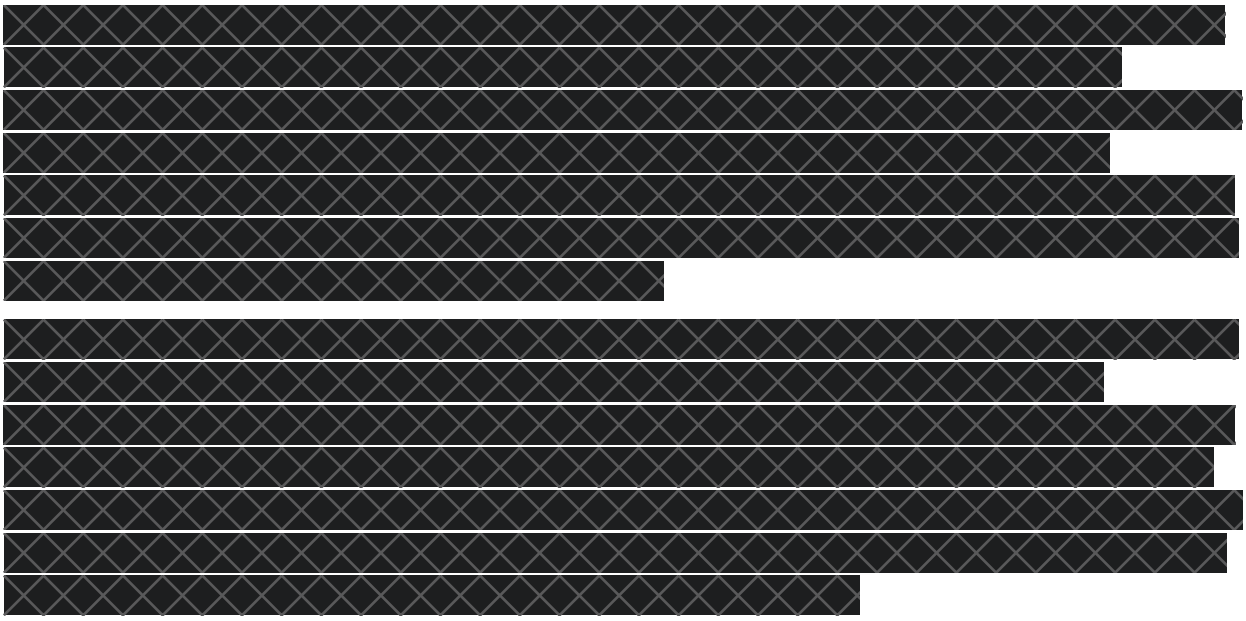
Refer to Cobimetinib US Package Insert for details and the most recent information.

More recently, as a class, MEK inhibitors are reported to incur a posterior segment toxicity, known as MEK-associated retinopathy (Stjepanovic 2016). Affected patients may describe decreased acuity, altered color perception, shadows, light sensitivity, metamorphopsia and glare. Findings on examination and ancillary testing (e.g. optical coherence tomography) include but

are not limited to neurosensory detachment, retinal pigment epithelial detachment, intraretinal edema, intraretinal cysts, vitelliform (exudative) findings, thickening or increased reflectivity of outer retina. Fortunately, these events tend to resolve, often spontaneously, and long term sequalae are rarely reported. The mechanism of toxicity appears to be mediated by MEK-induced alterations in retinal pigment epithelial barrier functions that prevent the accumulation of subretinal fluid (Duncan 2015, Weber 2016, De La Cruz-Merino 2017, Tyagi 2018, Méndez-Martínez 2019).

2.3.1.3. Potential Risks of RMC-4630 and Cobimetinib Combination

The combination of RMC-4630 and cobimetinib has not been previously administered in humans. Overlapping toxicities are anticipated. The nonclinical toxicity findings identified with repeat daily dosing of RMC-4630 are largely similar to those described for cobimetinib. In general, toxicities are also predicted to be dose- and duration-dependent, monitorable and reversible. In combination, adverse events may also increase in frequency and severity with duration of therapy and/or manifest at lower individual dose of each drug.



2.3.1.4. Potential Risks of Osimertinib (for US Study only)

The most common adverse reactions (≥20%) in patients treated with osimertinib as reported in the FLAURA study were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with osimertinib; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), interstitial lung disease (ILD)/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with osimertinib. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT

interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with osimertinib. The most frequent adverse reaction leading to discontinuation of osimertinib was ILD/pneumonitis (3.9%). The most common laboratory abnormality worsening from baseline were lymphopenia (63%), anemia (59%), thrombocytopenia (51%), and neutropenia (41%) any grade. High grade worsening (grade 3 or 4) in lymphopenia was observed in 5.6% of patients, anemia and thrombocytopenia in 0.7% of patients, and neutropenia in 3.0% of patients (Tagrisso USPI).

Fatal adverse events occurred in 6 patients (2%) with osimertinib treatment which included pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia in 1 patient each. However, none of the fatal adverse events were assessed as related to the osimertinib. There were no fatal cases of torsades de pointes or prolongation of QT interval in patients treated with osimertinib (Soria 2018).

Warnings and Precautions as reported in the osimertinib USPI are as follows:

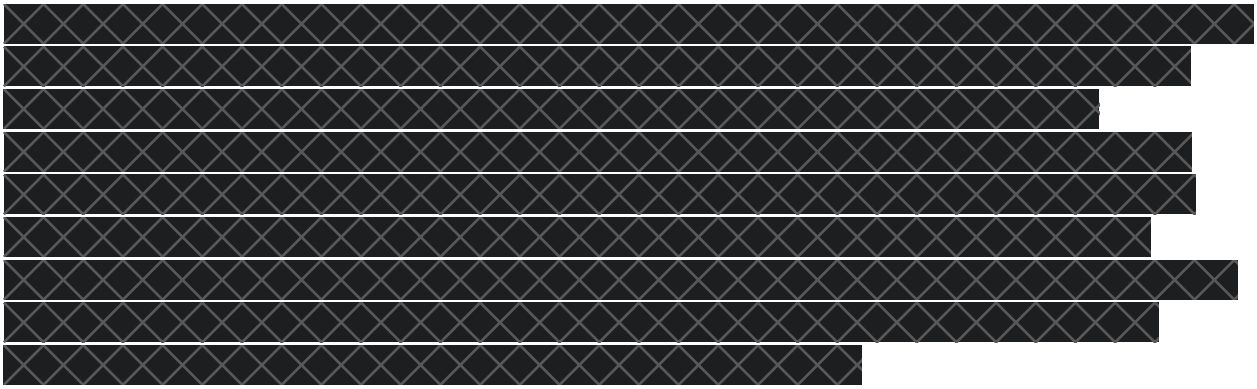
- **Interstitial Lung Disease/Pneumonitis:** Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 osimertinib-treated patients; 0.4% of cases were fatal. Withhold osimertinib and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue osimertinib if ILD is confirmed.
- **QTc Interval Prolongation:** Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with osimertinib. Of the 1142 patients treated with osimertinib in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Clinical trials of osimertinib did not enroll patients with baseline QTc of >470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue osimertinib in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.
- **Cardiomyopathy:** Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 osimertinib-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in LVEF ≥10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue osimertinib.

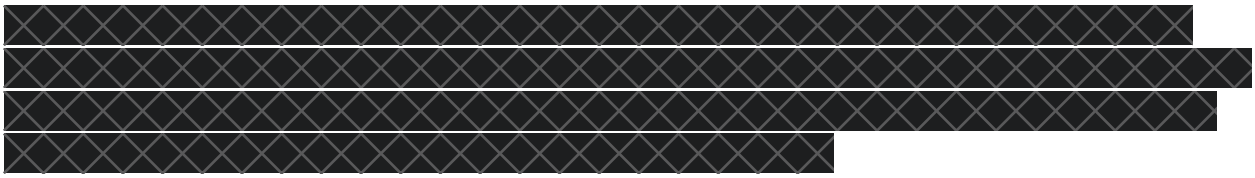
- **Keratitis:** Keratitis was reported in 0.7% of 1142 patients treated with osimertinib in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.
- **Erythema Multiforme and Stevens-Johnson syndrome:** Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving osimertinib. Withhold osimertinib if SJS or EMM is suspected and permanently discontinue if confirmed.
- **Embryo fetal toxicity:** Based on data from animal studies and its mechanism of action, osimertinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating osimertinib. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with osimertinib and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

Refer to Tagrisso (osimertinib) US Package Insert for more information

2.3.1.5. Potential Risks of RMC-4630 and Osimertinib Combination (for US Study Only)

The overlapping toxicities of a SHP2 inhibitor and an EGFR inhibitor have not been formally assessed in non-clinical models. As SHP2 is located downstream of EGFR receptor, both agents inhibit signaling in the RAS-MAPK signaling pathway and it is possible that overlapping toxicities may be observed.





2.3.2. Steps to Minimize Risk

Safety measures to minimize risks to participants have been incorporated in the design of the study. Eligibility criteria specifically exclude patients who may be at increased risk of predictable toxicities.

Safety monitoring (consisting of adverse events assessments, physical examinations, vital signs measurements, ECGs, clinical laboratory tests, Eastern Cooperative Oncology Group (ECOG) performance status, echocardiogram (ECHO)/multigated acquisition (MUGA) scans, and retinal examinations), will occur at regular intervals throughout the study. As a precaution, participants receiving strong CYP3A4 inhibitors (Appendix 8) and/or inducers are excluded until further data become available.

In addition to dose DLT criteria, dose modifications after the DLT window have been included in order to reduce the risk of toxicity while continuing to provide participants a potential treatment opportunity.

Invasive measures in this study are limited to venipuncture (all study participants) and tumor biopsies in participants when feasible. The primary purpose of the pre-treatment and on-study biopsies is to assess tumor biology and potential response to study intervention. The tumor tissue will also be used to explore predictive biomarkers (Section 8.7) (Hirsch 2003).

Two safety committees, a Dose-Escalation and Expansion Committee (“Dose Committee”) and an ISMC, will be used to monitor the safety of RMC-4630 monotherapy, RMC-4630 with cobimetinib combination, and RMC-4630 with osimertinib combination therapy. The Dose Committee is study-specific while the ISMC is RMC-4630 program-specific. The Dose Committee, comprising of Sponsor representatives and investigators, will evaluate the safety data throughout the study and provide recommendations regarding dose levels during the escalation phase as well as decide whether the Dose-Expansion Component may commence at the completion of a given Dose-Escalation Cohort. The ISMC will review emergent safety data at regular intervals for all participants during the course of the trial in conjunction with data from other active RMC-4630 trials. Refer to Section 8.3.6 for details.

3. OBJECTIVES AND ENDPOINTS

3.1. RMC-4630 and Cobimetinib Combination

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of the combination of RMC-4630 and cobimetinib in participants with relapsed/refractory solid tumors • To define the MTD and RP2D and schedules for the combination of RMC-4630 and cobimetinib in participants with relapsed/refractory solid tumors	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE v5 for the combination of RMC-4630 and cobimetinib • Incidence and nature of DLTs for the combination of RMC-4630 and cobimetinib
Secondary	
[redacted]	[redacted]
Tertiary/Exploratory	
[redacted]	[redacted]

3.2. RMC-4630 and Osimertinib Combination (Study in US Only)

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of the combination of RMC-4630 and osimertinib in participants with EGFR mutation-positive NSCLC who have progressed on or after osimertinib	• Incidence, nature, and severity of treatment emergent AEs and SAEs, graded according to the NCI CTCAE v5 for the combination of RMC-4630 and osimertinib
• To define the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D) and schedule for the combination of RMC-4630 and osimertinib in participants with EGFR mutation-positive NSCLC	• Incidence and nature of DLTs for the combination of RMC-4630 and osimertinib
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

The designs of two combination studies, RMC-4630 with cobimetinib and RMC-4630 with osimertinib, are described below.

4.1. Overall Design for RMC-4630 and Cobimetinib

This is an open-label, multicenter, Phase 1b/2 of oral RMC-4630 in combination with cobimetinib in participants with advanced relapsed/refractory solid tumors with *KRAS* amplification or harboring certain specific classes of mutations [redacted] and 2) RMC-4630 in combination with osimertinib in participants with epidermal growth factor receptor (EGFR) mutation-positive NSCLC.

This arm with RMC-4630 and cobimetinib will be conducted in US and ex-US countries. Prior to enrollment, all participants will undergo screening to determine study eligibility. Questions regarding eligible mutations may be addressed to the Sponsor. Information on tumor genotype will be collected on all participants. The following histotypes and genotypes will be enrolled in this study arm (Appendix 9A):

[redacted]

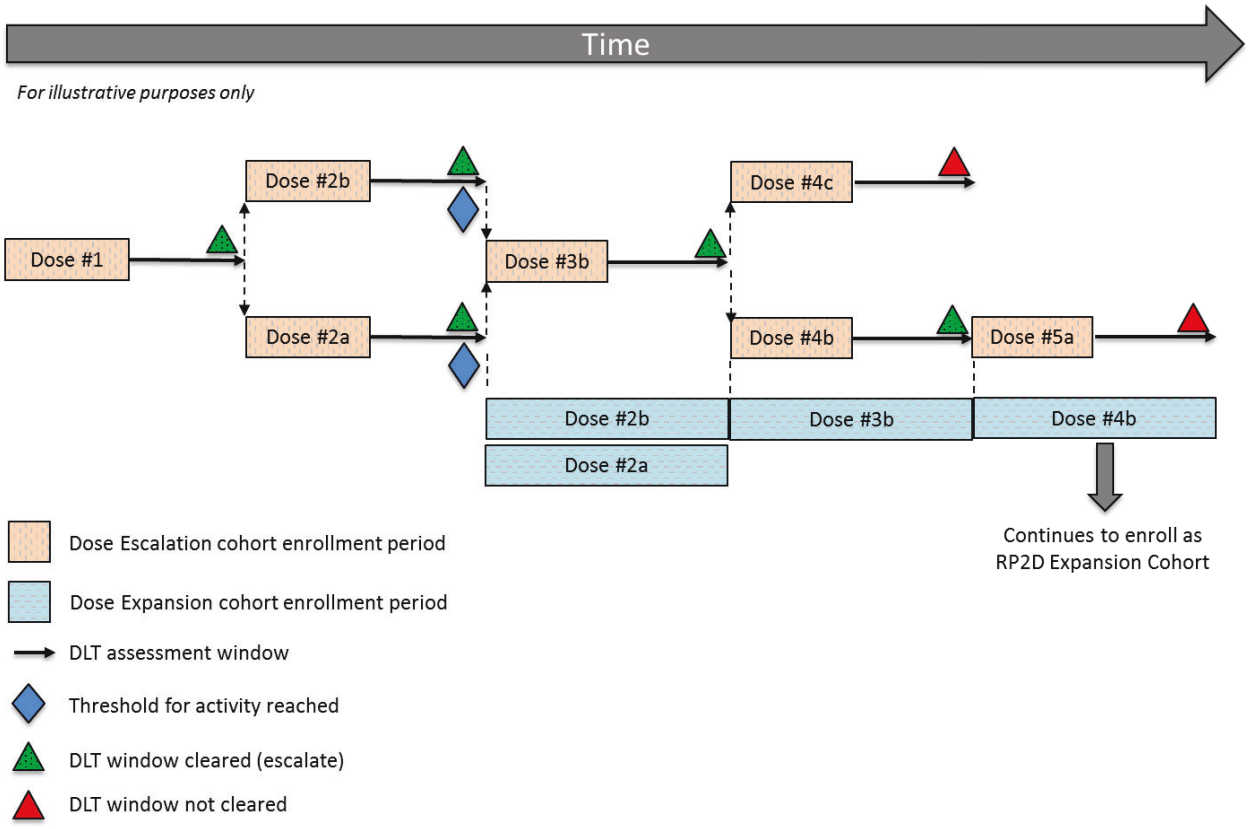
The presence of one or more of these tumor genotypes is required for enrollment. Eligibility will be assessed based on prior genomic testing using a clinically validated or qualified assay of tumor samples. ctDNA mutational analysis using a clinically qualified or validated test may also be used for enrollment. All local tumor genotyping analyses will be confirmed by central testing when tumor tissue is provided. A fresh biopsy will not be used to determine eligibility.

There will be two components to this arm: Dose-Escalation and Dose-Expansion. This arm will commence with the Dose-Escalation Component to determine the MTD and RP2D. A minimum of 3 participants will be enrolled at each dose combination level to evaluate for DLT events and identify the MTD. A Dose-Expansion cohort may follow each Dose-Escalation cohort below the RP2D. A final Dose-Expansion cohort will be evaluated at the RP2D. The purpose of the Dose-Expansion Component is to further evaluate the safety and tolerability of the combination of RMC-4630 and cobimetinib as well as assess preliminary signals of efficacy.

The Dose-Escalation and Dose-Expansion Components may enroll simultaneously but will have staggered start times such that the dose cohort within the Dose-Expansion Component will always enroll at the dose level below that of the actively enrolling cohort in the Dose-Escalation Component. The current Dose-Expansion Cohort will close to enrollment once the DLT window has been completed for the next higher dose level in the Dose-Escalation Component. At that point, a new Dose-Expansion Cohort will open for enrollment at this next higher dose level. The staggered enrollment between the Dose-Escalation and Dose-Expansion Cohorts is illustrated in Figure 6. After determination of the RP2D, further expansion will occur at the RP2D.

The diagram in Figure 6 below illustrates staggered enrollment for Scenario 1 in Figure 2.

Figure 6 Staggered Enrollment Between Dose-Escalation and Dose-Expansion Cohorts for RMC-4630 and Cobimetinib Study



Abbreviations: DLT, dose-limiting toxicity; PK, pharmacokinetic(s); RP2D, recommended Phase 2 dose.

MTD will be identified based on safety data during the DLT assessment period (Cycle 1; Section 4.1.1.1). The RP2D will be based on all available safety, PK, PD, and efficacy data for all participants at the end of the Dose-Escalation Component and any available data from the Dose-Expansion Cohorts.

The Dose Committee will evaluate the safety data during the DLT period and render decisions whether dose escalation may proceed and whether the Dose-Expansion Component may commence. The ISMC will review emergent safety data from the RMC-4630 program at regular intervals for all participants during the course of the trial in conjunction with data from other active RMC-4630 trials (Section 8.3.6).

4.1.1. Dose-Escalation Component

4.1.1.1. Dose-Escalation Design

The starting dose of RMC-4630 for twice weekly dosing schedule on D1, D4 is approximately 50% of the dose intensity of the highest cleared dose from the Phase 1 monotherapy study RMC-4630-01, (https://clinicaltrials.gov; NCT03634982).

Table 4 Starting Dose of RMC-4630

[a]

[redacted]

Table 5 Primary Dose Levels for RMC-4630

[redacted]

In addition to the planned dose levels, alternative schedules which allow D1, D2 dosing of either or both RMC-4630 and cobimetinib may be initiated and the starting dose will be based on the analysis of emerging safety and PK data. Therefore, RMC-4630 can be administered in either a D1, D4 or D1, D2 schedule. Whereas, cobimetinib can be administered in either once daily (21/7) or D1, D2 schedule. However, the single and monthly starting dose for cobimetinib will not exceed those already tested in clinical trials. The decision to trigger exploration of an alternative schedule will be made by the Dose Committee after careful review of emerging toxicity profile of the combination.

The first cycle (eg, 28 days) constitutes the DLT assessment period. The first participant in the initial combination dose level will be observed for the first 7 days of dosing prior to dosing additional participants in this cohort. Following this 7-day observation period, additional participants may be enrolled in the cohort. In subsequent combination dose level cohorts, participants may be enrolled concurrently.

4.1.1.2. Dose-Limiting Toxicity Criteria

DLT is defined as any one of the following toxicities considered by the investigator to be related to study treatment:

- Grade ≥4 adverse events (AEs)
- Grade 3 febrile neutropenia or hemorrhage
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 3 non-hematologic AEs, including rash, nausea/vomiting, hypertension, diarrhea, retinopathy, or blurred vision that remain uncontrolled (does not resolve to ≤ Grade 2) for

>72 hours despite maximal supportive care. Electrolyte abnormalities or Grade 3 asymptomatic CPK or GGT elevations that is corrected within 72 hours will not be considered DLTs.

- Grade 3 AST, ALT, and/or total bilirubin elevations that persist >5 days
- Concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or international normalized ratio (INR) >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case)
- Grade 3 QTcF (defined as QTc using Fridericia's formula [QTcF] >500 msec OR change from baseline of QTcF >60 msec) prolongation based on a triplicate ECG
- Retinal vein occlusion (RVO) any grade
- 50% or less dose intensity of RMC-4630 (eg, miss ≥4 doses) and/or cobimetinib (eg, miss ≥10 doses if cobimetinib is dosed daily during 21/7 schedule or miss ≥4 doses if cobimetinib is dosed intermittently on D1, D2) due to study drug related toxicity
- Ejection fraction <50% with an absolute decrease of >10% from baseline

4.1.1.3. Dose-Escalation Rules

Dose escalation will be guided using a CRM model (Appendix 10) to determine the MTD of the combination of RMC-4630 and cobimetinib. This CRM is an adaptive dose escalation approach based on a Bayesian statistical model to assess the MTD for drug combinations as a function of their doses. [redacted] The MTD is selected as the combination associated with the highest posterior probability of DLT rating within the target interval of 25% - 35% with a target DLT rate of 30%, and which have been used to treat at least 6 participants. If alternative dosing schedule(s) are evaluated, a separate CRM model will be set up using the same modeling structure but potentially different parameters according to the updated prior knowledge of the safety of the alternative dosing schedule(s).

During the escalation period, participants will be enrolled in a series of cohorts for each combination dose level. A minimum of 3 participants are required on a combination dose level to be DLT evaluable and to render a decision to proceed to the next dose level. A 4th participant, if available, may enroll onto the escalation dose before the first 3 participants have completed the DLT evaluation. However, in the case a 4th patient is enrolled in a cohort, dose escalation decision will take place after the first 3 patients have completed the DLT assessment period.

Once the DLT status of the 4th patient is available, and if this patient experiences a DLT after dose escalation decision and enrollment of the subsequent dose level, the Sponsor will rerun the Bayesian model and the Dose Committee will re-evaluate the dose escalation recommendation and continuation of treatment at the subsequent dose level. If a participant experiences a DLT, additional participants will be enrolled at that dose. The cohort at the MTD will include at least 6 participants.

A participant will be DLT non-evaluable in either of the following 2 scenarios where a replacement participant(s) will be enrolled:

1. Receives less than 75% of planned dose of cobimetinib (miss ≥ 3 doses of cobimetinib on D1D2 intermittent schedule and ≥ 6 doses of cobimetinib on 21 on/7 off schedule within the DLT window) for reasons other than toxicity
2. Misses 3 or more consecutive or non-consecutive doses of RMC-4630 within the DLT window for reasons other than toxicity

Moving to a higher dose of both agents is not allowed. Moving to a higher dose of one agent and a lower dose of the other agent is allowed. Skipping a dose level as specified above is not allowed, but intermediate dose levels of RMC could be explored. Parallel dose cohorts may be allowed if the collective safety data are supportive (Appendix 10). The data in both Dose-Escalation and Dose-Expansion Components (Section 4.1.1, Section 4.1.2) will be combined to fit the model and determine the recommended dose combination to treat the next cohort of patients.

The Dose Committee will be responsible for evaluating the safety data during the DLT period and provide decisions regarding the actual dose escalation level based on safety data, updated model dose recommendations, and other relevant available information. The RP2D will be determined by the Sponsor based on the totality of the information available at all dose levels, combining the Dose-Escalation and Dose-Expansion Components, and should not exceed the MTD. The Dose Committee will determine regarding opening the Dose-Expansion Component.

4.1.2. Dose-Expansion Component

Once a combination dose level during the Dose-Escalation phase has reached a threshold level of activity based on clinically meaningful reduction in tumor burden at a dose with acceptable toxicity, additional participants may possibly be enrolled at dose levels prior to the determination of RP2D. The Dose Committee will determine whether clinically meaningful reduction has been achieved (eg, ≥30% reduction in the sum of longest diameters of target lesions or a lesser diminution with a preponderance of clinical evidence of benefit). The decision to open the Dose-Expansion Component will be made by the Dose Committee. See Dose-Escalation and Expansion Committee Charter for more information.

Multiple Dose-Expansion and Escalation Cohorts may occur in parallel. The current Dose Expansion Cohort will stop enrollment after the next higher dose combination in the Dose Escalation Component is completed. [redacted]

In the case of parallel Dose-Expansion cohorts below the RP2D, slot assignment to parallel cohorts will be in an alternating manner. Please refer to Figure 1.

The MTD and RP2D will be determined after the Dose-Escalation and the Dose-Expansion (below the RP2D) Components are completed. [redacted]

4.1.3. Intra-participant Dose-Escalation

Intra-participant dose escalation may be allowed to provide patients with an opportunity to receive a higher dose to potentially derive greater benefit from RMC-4630 and cobimetinib combination. Participants will be allowed to escalate to a higher dose once it has been cleared by the Dose Committee. For intraparticipant dose escalation to occur, the request must be approved by the sponsor Medical Monitor. Additionally, the following criteria must be met:

- Participants should be able to tolerate the dose level at which they are enrolled, demonstrated by minimal dose holds and no dose reductions (Section 6.6.2). Participants who have previously had a ≥Grade 3 adverse event during the study will not be eligible for dose escalation unless the adverse event was clearly unrelated to study drugs. Low grade, ongoing adverse events will be evaluated on case-by-case basis and may restrict participant's eligibility to escalate.
- Participants should complete at least 2 cycles of treatment at the dose level cohort in which they were first enrolled into the study. In rare cases, a participant may be allowed to dose-escalate without completing 2 cycles of the treatment upon discussion with the Medical Monitor. A dose cannot be escalated before the DLT window ends.
- If there are two higher combination dose levels which are cleared by the dose committee, then the participant will be allowed to escalate to the highest dose level which was cleared by the Dose Escalation and Expansion Committee. If two higher parallel cohorts are being evaluated, the investigator–after discussion with the Medical Monitor–will determine which combination dose level the participant may escalate to.

After intraparticipant dose escalation occurs, if a participant experiences an AE that meets the definition of a DLT at the dose level which has already been cleared, the participant should be managed according to the dose modification guidelines specified in Section 6.6.2. For any Grade 4 toxicities, treatment with RMC-4630 and cobimetinib should be discontinued.

4.1.4. Duration of Therapy

Participants will be permitted to remain on-study therapy until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met (Section 7.1 and Section 7.2), or end of study (Section 4.3), whichever occurs first. Participants will return to the clinical site for an EOT visit within 30 days after last treatment dose. Alternatively, participants may withdraw from the study at any time with or without cause and will be encouraged for EOT evaluation.

After termination of treatment, participants will continue on study for long-term survival follow-up every 3 months (±2 weeks), unless they withdraw consent for further follow-up or end of study.

The anticipated duration of the study is approximately 3 years, including 2 years of enrollment and 1 year of follow-up visits.

4.1.5. Scientific Rationale for Study Design

The first phase constitutes a Dose-Escalation Component, which has been designed to minimize the number of participants exposed to potentially subtherapeutic doses.

After the dose level achieves a threshold for activity (Section 4.1), Dose-Expansion Cohorts may be initiated. In the Dose-Escalation Component, assessment of safety and tolerability will be the primary endpoints and will be directly measured by the incidence of DLTs, AEs, and serious adverse events (SAEs).

The Dose-Expansion Component below the RP2D provides a further assessment of safety and the tolerability, PK, and PD effects, as well as the preliminary activity of RMC-4630 and cobimetinib combination therapy at potentially active doses. The Dose-Expansion Component is designed such that multiple cohorts below the RP2D will be assessed and will provide additional information on the therapeutic index of RMC-4630 and cobimetinib, including any potential differential impact of dose based on genotype and histotype.

For the RMC-4630 and cobimetinib arm, there is a concurrent but staggered enrollment strategy between the Dose-Escalation and Dose-Expansion Components. The Dose-Expansion Component begins only once a threshold for activity has been demonstrated during the Dose-Escalation Component (Section 4.1). Once a cohort in the Dose-Escalation Component has completed the DLT window, a Dose-Expansion Cohort at that dose may open at the same time as the next highest dose cohort in Dose-Escalation Component.

4.1.6. Justification for Starting Dose

Justification for Starting Intermittent Dosing Schedule for RMC-4630

Preclinical testing of intermittent dosing schedules was performed in the NCI-H358 xenograft model of *KRAS*^{G12C} mutant NSCLC.

Justification for Starting Intermittent Dosing Schedule for Cobimetinib

Justification for Starting Dose

The starting dose for RMC-4630 for D1, D2 schedule will be decided based on the emerging toxicity profile of the combination and will be decided by the Dose Committee. [redacted]

[redacted]

The starting dose for cobimetinib for D1, D2 schedule will be decided based on the emerging toxicity profile of the combination and will be decided by the Dose Committee. [redacted]

[redacted]

Justification for RMC-4630 dose reduction to 100 mg D1D2 (if needed) in the Final Expansion Phase:

[redacted]

4.2. RMC-4630 and Osimertinib Design (Study in US Only)

This arm with RMC-4630 and osimertinib will be conducted ONLY in the US. This is an open-label, Phase 1b exploratory study of RMC-4630 in combination with osimertinib in participants with epidermal growth factor receptor (EGFR) mutation-positive NSCLC.

Prior to enrollment into this arm, all participants will undergo screening to determine eligibility. Information regarding existing mutations at baseline will be collected using prior histological or ctDNA documentation for EGFR mutations. Sponsor will determine eligibility based on the presence of an *EGFR* mutation in the most recent genomic report for the dose escalation component of the study. The following mutations/histologies will not be eligible to enroll:

[redacted]

Eligibility into Dose Escalation: Eligibility will be assessed based on *current* genomic testing report either from tumor biopsy or ctDNA which confirms the presence of an EGFR mutation. The report should ideally be obtained at the time of progression on osimertinib or at the time of progression on most recent prior therapy if osimertinib is not the most recent prior therapy. Participants who received intervening chemotherapy or any other therapy after progression on Osimertinib will be eligible as long as the presence of EGFR mutation is noted on the most recent genomic report. The samples should have been tested using a clinically validated or qualified assay for tumor or blood samples which includes NGS, IHC, FISH or PCR. If the patient does not have an EGFR mutation either based on the tumor biopsy or ctDNA report, then the patient will be considered ineligible for participation.

There are two components in this arm: Dose-Escalation Phase and Dose-Expansion Phase. Enrollment in Dose-Expansion will be initiated after Dose-Escalation has ended and an MTD or RP2D has been established with the combination treatment.

Table 6 Dose Escalation Rule of the Modified Toxicity Probability Interval-2 Method

C) If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless there is unacceptable high toxicity, at which point terminate the study for safety. If the decision based on the new cohort at the lowest dose still recommends dose de-escalation, new dose levels may be explored.

D) If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose. If the decision based on the new cohort at the highest dose still recommends dose escalation, new dose levels may be explored.

E) At least 6 patients have to be treated at the recommended dose level, before declaring it the MTD.

F) Skipping dose is not allowed.

Once an MTD or RP2D is determined, Dose-Expansion Component will commence to further evaluate the safety and tolerability of the combination of RMC-4630 and osimertinib as well as assess preliminary signals of efficacy. The MTD or RP2D will be based on all available safety, PK, PD, and efficacy data for all participants at the end of the Dose-Escalation Component, and Dose-Expansion will only begin after Dose-Escalation is complete.

Eligibility into Dose-Expansion – Will be determined using existing reports (either from tumor sample or ctDNA). On the most recent genomic report post Osimertinib progression, patient should have a mutation of interest as outlined in Appendix 9B for eligibility. If patient does not have a mutation of interest either using ctDNA or tumor biopsy, then they would be deemed ineligible to participate in Dose-Expansion (See Appendix 9B). On-study fresh-tumor biopsies for biomarker analyses will be mandatory for each Dose-Expansion participant unless the investigator determine that the tumor site is not amenable to biopsy and poses a significant risk to patient safety. The Sponsor will evaluate this requirement on a case-by-case basis. An EOT tumor biopsy will be requested but will not be mandatory for patients in Dose-Expansion component.

Participants enrolled in the Dose-Escalation Phase or Dose-Expansion Phase will undergo regular safety assessments including physical examinations and laboratory testing. [redacted]

4.2.1. Dose-Escalation Component

4.2.1.1. Dose-Escalation Design

RMC-4630 will be administered on an intermittent schedule throughout each 28-day cycle. Dose escalation will be conducted using a mTPI2 design to determine the MTD.

[redacted] The decision for the initial dose/schedule of RMC-4630 was made by the Dose Committee after careful evaluation of safety data.

[redacted]

The first cycle (eg, 28 days) constitutes the DLT assessment period. The first participant in the initial combination dose level will be observed for the first 7 days of dosing prior to dosing additional participants in this cohort. Following this 7-day observation period, additional participants may be enrolled in the cohort. In subsequent combination dose level cohorts, participants may be enrolled concurrently.

4.2.1.2. Dose-Limiting Toxicity Criteria

DLT is defined as any one of the following toxicities considered by the investigator as related to study treatment:

Hematologic

- Grade 4 neutropenia or thrombocytopenia lasting >7 days
- Grade ≥3 febrile neutropenia
- Grade ≥3 hemorrhage
- Grade ≥3 thrombocytopenia with clinically significant bleeding

Non-hematologic

- Grade ≥4 non-hematologic adverse events (AEs)
- Retinal vein occlusion
- Grade 3 heart failure
- Grade ≥2 pneumonitis
- Grade 3 fatigue lasting >7 days
- Grade 3 hypertension or rash which does not improve or remains uncontrolled for >5 or more days despite maximal supportive care
- Other Grade 3 nonhematologic AEs, including photosensitivity, nausea/vomiting, diarrhea, retinopathy, blurred vision, or corneal ulceration which does not improve or remains uncontrolled (does not resolve to ≤Grade 2) for >72 hours despite maximal supportive care. Electrolyte abnormalities that are corrected within 72 hours will not be considered DLTs
- Grade ≥3 AST, ALT, and/or total bilirubin elevations which does not improve or remains uncontrolled >5 days
- Concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law)
- Grade 3 QTcF (defined as QTc using Fridericia's formula [QTcF] >500 msec OR change from baseline of QTcF >60 msec) prolongation based on a triplicate ECG
- 50% or less dose intensity of RMC-4630 (eg, miss ≥4 doses for twice-weekly (BIW) schedule) and/or osimertinib (ie, miss ≥14 doses for QD schedule) due to study drug related toxicity

4.2.1.3. Dose-Escalation Rules

In the event a participant discontinues treatment prior to completion of the first cycle (DLT window), receives less than 75% of planned dose of osimertinib (defined as missing 8 or more consecutive or non-consecutive doses of osimertinib), receives less than 75% of planned dose of RMC-4630 (defined as missing 3 or more consecutive or non-consecutive doses of RMC-4630) for reasons other than toxicity, a replacement participant will be enrolled for a minimum of 3 DLT evaluable participants.

The Dose Committee will be responsible for reviewing and evaluating the safety, efficacy data and other relevant available information (PK or biomarker data) during the DLT period and provide a final decision regarding the next dose escalation level. The RP2D will be determined

by the Sponsor based on the totality of the information available at all dose levels and should not exceed the MTD. If 2 or more DLTs are observed beyond the DLT assessment period (ie, a delayed DLT) within a Dose-Escalation Cohort, further enrollment may be stopped pending safety analysis of the events. These events will not affect the determination of the MTD but will be used in determining the appropriate RP2D. Further details on the Dose Committee are provided in Section 8.3.6. The Sponsor will determine regarding opening the Dose-Expansion Component.

The ISMC will conduct regular safety data reviews of emergent data from the RMC-4630 program as well as ad hoc emergent safety data reviews for all participants across RMC-4630 trials.

4.2.2. Dose-Expansion Component

Once a combination dose level during the Dose-Escalation phase has reached an MTD, the Dose committee will determine whether Dose-Expansion phase should be initiated and will determine the RP2D which may or may not be the same as MTD but would not exceed the MTD.

The Dose-Expansion phase may enroll 6-18 participants depending on how many participants will enroll in the Dose Escalation portion for a total of 24 participants in the RMC-4630 + osimertinib study arm. Please refer to Section 4.2 for eligibility.

4.2.3. Intra-participant Dose-Escalation

Participants may be allowed to escalate to a higher dose once it has been cleared by the Dose Committee and is deemed safe and tolerable. For intraparticipant dose escalation to occur, the request must be approved by the sponsor Medical Monitor.

4.2.4. Duration of Therapy

Participants will be permitted to remain on-study therapy until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met (Section 7.1 and Section 7.2), or end of study (Section 4.3), whichever occurs first. Participants will return to the clinical site for an EOT visit within 30 days after last treatment dose. Alternatively, participants may withdraw from the study at any time with or without cause and will be encouraged for EOT evaluation.

After termination of treatment, participants will continue on study for long-term survival follow-up every 3 months (±2 weeks), unless they withdraw consent for further follow-up or end of study.

The anticipated duration of the study is approximately 3 years, including 2 years of enrollment and 1 year of follow-up visits.

4.2.5. Scientific Rationale for Study Design

The first phase constitutes a Dose-Escalation Component, designed to understand the safety and tolerability of RMC-4630 in combination with osimertinib and determine the MTD and RP2D for this combination while also minimizing the number of participants exposed to potentially subtherapeutic doses. Given that osimertinib is an approved treatment for NSCLC with an EGFR mutation, only RMC-4630 [redacted]

In the Dose-Escalation Component, assessment of safety and tolerability will be the primary endpoints and will be directly measured by the incidence of DLTs, AEs, and serious adverse events (SAEs).

Since the primary objective of the study is to understand the safety and tolerability of this combination and the proposed sample size is limited to 24 participants, there will be no Dose-Expansion Component below the RP2D for this combination. Once the combination dose level during Dose-Escalation has reached an MTD, initiation of final Dose-Expansion at RP2D would then be determined by the Dose Committee.

4.2.6. Justification for Starting Dose

[redacted]

4.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study (ie, last participant, last visit [LPLV]) or 12 months after the last participant receives the first dose of study treatment, whichever occurs first.

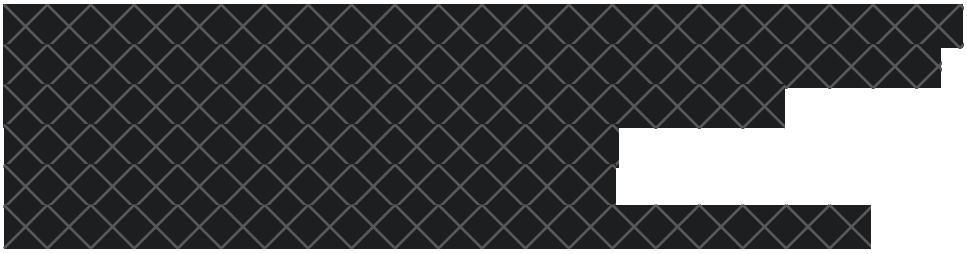
5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

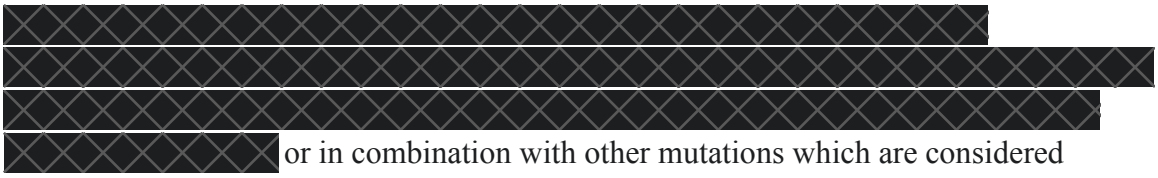
5.1. Inclusion Criteria

For RMC-4630 + Cobimetinib only:

1. Participants who have advanced solid tumors that have failed, are intolerant to or are considered ineligible for standard of care anti-cancer treatments including approved drugs for oncogenic drivers in their tumor type (eg, participants with NSCLC and KRAS mutations must have received or been offered treatment with platinum-based chemotherapy **OR** a PD-1 or PD-L1 inhibitor).
2. Participants must have one of the following molecular aberrations and specific histotypes:



For RMC-4630 + Osimertinib only:

1.  or in combination with other mutations which are considered sensitive to SHP2 inhibition (for dose expansion only) at any time since the initial diagnosis of NSCLC (see Appendix 9B for a list of mutations eligible for dose expansion)
2. Evidence of radiological documentation of progression with osimertinib monotherapy or an osimertinib containing regimen. Participants should not be considered a current candidate for 1st generation EGFR TKIs by the investigator.
3. Previously able to tolerate osimertinib 80 mg QD and no current Grade 2 or greater AE attributable to osimertinib

All participants must meet ALL of the following inclusion criteria:

1. Age ≥18 years
2. Evaluable or measurable disease per RECIST v1.1 criteria for Dose-Escalation; measurable disease (only) per RECIST v1.1 for Dose-Expansion
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 with no deterioration over the previous 2 weeks
4. Adequate hematological and organ function, confirmed by the following laboratory values at local investigative site:
    - Bone Marrow Function
    - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L without transfusion support
    - Hemoglobin ≥9 gm/dL
    - **Hepatic Function**
        - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN)
        - Bilirubin ≤1.5 × ULN (<3.0 mg/dL if participant has Gilbert's disease)
    - **Renal Function**
        - Blood creatinine ≤1.5 × ULN or creatinine clearance of >50 mL/min (using Cockcroft-Gault formula or 24-hour urine collection)
    - **Coagulation**
        - Prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT/PTT) <1.3 × ULN (or partial thromboplastin time (PTT)) or within therapeutic range if receiving therapeutic anticoagulation that would affect the PT/INR.
5. Capable of giving signed informed consent. Willing and able to compile with study requirements and restrictions.
6. Life expectancy ≥12 weeks
7. Females of childbearing potential must agree to always use 2 effective forms of contraception during the course of the study and for at least 3 months after completion of study therapy.
8. Males with partners of childbearing potential must agree to always use 2 effective forms of contraception during the course of the study and for at least 3 months after completion of RMC-4630 and cobimetinib or 4 months after completion of RMC-4630 and osimertinib.
9. Negative blood pregnancy test within 14 days of commencement of study medications in women of childbearing potential.

5.2. Exclusion Criteria

ANY of the following criteria will exclude participants from study participation:

1. Excluded genotypes for both cobimetinib and osimertinib arms (including co-occurring mutations for both dose escalation and dose expansion):
   - [redacted]
2. For RMC-4630 + cobimetinib arm, [redacted]
3. For RMC-4630 + osimertinib arm: [redacted]
4. [redacted]
5. [redacted]
   - **For RMC-4630 + osimertinib arm**: [redacted]
6. History of cerebrovascular stroke or transient ischemic attack within previous 6 months.
7. The following ocular abnormalities are excluded:
   - History or current retinal pigment epithelial detachment (RPED), central serous retinopathy, retinal vein occlusion (RVO), neovascular macular degeneration, or factors considered by the investigator to present an unacceptable risk of RPED or RVO.
   - Visible retinal pathology as assessed on ophthalmic examination that is considered a significant risk factor for RVO or RPED by an ophthalmologist
   - **For RMC-4630 + osimertinib arm**: any evidence of current keratitis

8. Any of the following cardiovascular abnormalities:
    i. Medically uncontrolled hypertension (eg, ≥160 mm Hg systolic or ≥100 mm Hg diastolic)
    ii. Acute coronary syndrome (eg, unstable angina, coronary artery stenting, or angioplasty, bypass grafting) within prior 6 months
    iii. History or current uncontrolled clinically significant unstable arrhythmias
    iv. Participants who have pacemakers to control atrial arrhythmias are candidates for the study. Participants with medically controlled atrial fibrillation >1 month prior to C1D1 are eligible.
    v. History of congenital long QT syndrome or prolonged QTcF interval >480 ms using Fridericia's formula (unless a pacemaker is in place) or uncorrectable abnormalities in blood electrolytes (sodium, potassium, calcium, magnesium, phosphorus).
    vi. Left ventricular ejection fraction (LVEF) < institutional LLN or <50%, whichever is lower.
    vii. Symptomatic congestive heart failure, New York Heart Association Class II or higher
9. Active, clinically significant interstitial lung disease or pneumonitis
    - **For RMC-4630 + osimertinib arm:** participants with a past medical history of interstitial lung disease (ILD), drug induced ILD, radiation pneumonitis which required steroid treatment, or evidence of clinically active ILD will be excluded
10. Grade ≥2 proteinuria
11. Active autoimmune disease requiring systemic treatment within past 6 months (ie, with use of disease modifying agents, non-physiologic doses of corticosteroids or immunosuppressive drugs); includes current autoimmune sequelae or previous Grade > 2 autoimmune sequelae from checkpoint inhibitors or other immunomodulatory treatments which requires systemic therapy. Participants with autoimmune endocrinopathies on hormonal supplementation may enroll if approved by the Medical Monitor.
12. Known HIV infection or active/chronic Hepatitis B or C
13. Known history of bleeding diathesis
14. Inability to swallow tablets/ capsules or impairment of gastrointestinal function that may alter the absorption of RMC-4630, cobimetinib or osimertinib (eg, uncontrolled nausea and vomiting, diarrhea, malabsorption syndrome, inflammatory bowel disease, gastrectomy, small bowel resection)
15. History of severe allergic reaction to any of the study intervention components
16. Patients receiving specific oncologic therapies are excluded:
    a. Treatment with chemotherapy or biologics/monoclonal antibodies <21 days of C1D1

b. Treatment with radiation therapy <14 days of C1D1

c. Treatment with TKI, hormonal therapy (except megesterol acetate) <7 days of C1D1

   i. For RMC-4630 + osimertinib arm: Osimertinib can continue uninterrupted during screening.

d. Treatment with immunotherapy (eg, checkpoint inhibitors) <14 to 28 days of C1D1 of immunotherapy depending on specific immunotherapy agent and duration of treatment

e. Treatment with *KRAS*^{G12C} inhibitors, MEK inhibitors, and/or SHP2 inhibitors including RMC-4630 < 21 days of C1D1

f. Treatment with all other anti-cancer treatments including investigational agents that do not fit in the above categories <21 days of C1D1

17. Major surgery ≤28 days prior to C1D1. In all cases, the patient must be sufficiently recovered and stable before treatment administration.

18. Medication and supplements that may interfere or potentiate with RMC-4630, cobimetinib or osimertinib metabolism or toxicity PRIOR or DURING study intervention are excluded:

19. Females who are pregnant or breastfeeding

20. Any other unstable or clinically significant concurrent medical condition (eg, substance abuse, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism, etc.) that would, in the opinion of the investigator, jeopardize the safety of a participant, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of grapefruit or grapefruit-containing products, or Seville oranges from 7 days before the start of study intervention until after the final dose.

Fasting (except water) 1 hour prior to and 1 hour after each RMC-4630 dose is required. Fasting is **NOT** required for cobimetinib; however, on days when both medications are taken together, fasting is requisite due to the requirements of RMC-4630. Similarly, fasting is NOT required for osimertinib; however, on days when both medications are taken together, fasting is requisite due to the requirements of RMC-4630.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently able to receive treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (ie, screen failure) may be rescreened within 5 days of the initial screening date of screen failure. Rescreened participants should be assigned the same participant number as for the initial screening. Only hematology, chemistry, and coagulation tests may need to be repeated if outside the screening window. Other clinical testing will not need to be repeated if outside screening window (ie, within 5 days).

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

6.1.1. RMC-4630 and Cobimetinib

[redacted]

In addition to the planned dose levels, alternative dose schedules which allow D1, D2 dosing of either or both RMC-4630 and cobimetinib may be initiated and the starting dose will be based on

the analysis of emerging safety and PK data. Therefore, RMC-4630 can be administered in either a D1, D4 or D1, D2 schedule. Whereas, cobimetinib can be administered in either once daily (21/7) or D1, D2 schedule. However, the single and monthly starting dose for cobimetinib will not exceed those already tested in clinical trials. The decision to trigger exploration of an alternative schedule will be made by the Dose Committee after careful review of emerging toxicity profile of the combination.

RP2DS for final expansion is RMC-4630 140 mg on D1D2 and cobimetinib 40 mg on D1D2.

The tablets and capsules should not be crushed or chewed. The participant should administer the study intervention approximately the same time every day except for clinic visit days as listed in the SoA (Section 1.3). On these clinic visits, the participant should await instruction from the study staff to coordinate with the timing of PK and/or PD sampling.

6.1.2. RMC-4630 and Osimertinib (Study in US Only)

During the Dose Escalation Component, RMC-4630 will be administered orally on an intermittent basis with twice weekly dosing on D1 and D2 with a starting dose of 140 mg. Alternative dose schedule for RMC-4630 including D1D4 dosing may be explored depending on emerging data from this study and other RMC-4630 studies. Osimertinib will be dosed orally on the approved monotherapy dose and schedule of 80 mg once daily. The tablets and capsules should not be crushed or chewed. The participant should administer the study intervention approximately the same time every day except for clinic visit days as listed in the SoA (Section 1.3).

Dosing in the Dose-Expansion Component of RMC-4630 will be determined from the respective Dose-Escalation Component.

The participant is expected to administer a dose twice weekly on D1 and D2 (or D1D4 if an alternative schedule is implemented) except clinic visit days as listed in SoA. On these clinic visits, the participant should await instruction from the study staff to coordinate with the timing of PK and/or biomarker sampling.

Table 7 Study Interventions Administered: RMC-4630 and Cobimetinib

Component Name	Dose-Escalation and Dose-Expansion
Intervention Name	RMC-4630 and Cobimetinib
Type	Drugs
Dose Formulation	RMC-4630: [redacted] Cobimetinib: Film-coated Tablet
Unit Dose Strength(s)	[redacted]
Dosage Level(s)	[redacted]
Route of Administration	Oral with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration for RMC-4630 alone or RMC-4630 in combination with cobimetinib. No restrictions for cobimetinib when taken alone
Investigational Product	RMC-4630 Cobimetinib
Sourcing	RMC-4630 [redacted] Cobimetinib: Supplied by Roche
Packaging and Labeling	[redacted] Cobimetinib: Supplied as 63-count in HDPE bottles, overlabeled
Current/Former Name(s) or Alias	RMC-4630, [redacted] COTELLIC®, cobimetinib, cobimetinib fumarate

Abbreviations: CMO, contract manufacturing organization; HDPE, high-density polyethylene; PIC, powder-in-capsule.

Table 8 Study Interventions Administered: RMC-4630 and Osimertinib

Component Name	Dose-Escalation and Dose-Expansion
Intervention Name	RMC-4630 and Osimertinib
Type	Drugs
Dose Formulation	RMC-4630: [redacted] Osimertinib: Film-coated Tablet
Unit Dose Strength(s)	[redacted]
Dosage Level(s)	[redacted]
Route of Administration	Oral with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration for RMC-4630 alone or RMC-4630 in combination with osimertinib. No restrictions for osimertinib when taken alone
Investigational Product	RMC-4630 Osimertinib
[redacted]	RMC-4630: [redacted] Osimertinib: Commercially available via pharmacy
Packaging and Labeling	RMC-4630: Study drugs (PIC drug products) are packaged in [redacted] Osimertinib: Supplied as 30-count in HDPE bottles
Current/Former Name(s) or Alias	RMC-4630, RMC[redacted] TAGRISSO®, osimertinib, osimertinib mesylate, mereletinib

Abbreviations: CMO, contract manufacturing organization; HDPE, high-density polyethylene; PIC, powder-in-capsule; QD, daily.

6.2. Preparation/Handling/Storage/Accountability

RMC-4630 [redacted] are packaged in high-density polyethylene (HDPE) bottles with open labeling and are shipped and stored [redacted]

Cobimetinib (COTELLIC®) is shipped and stored [redacted]

Osimertinib (TAGRISSO®) is shipped and stored at 15°C to 30°C (59-86°F).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive RMC-4630 or cobimetinib and only authorized site staff may supply study intervention. Osimertinib will be supplied by the local pharmacy. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the study Pharmacy and Investigational Product Administration Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study without randomization. In order to minimize bias, the participants will be assigned sequentially as they are enrolled into the study using the inclusion and exclusion criteria as outlined in Section 5.1 and Section 5.2. Enrollment will be confirmed by the sponsor Medical Monitor after review of all supporting documentation for eligibility criteria.

The following guidelines will be considered for enrollment and cohort assignment for participants enrolled in the RMC-4630 and cobimetinib cohort:

- Once the Dose-Expansion Component commences, enrollment into the Dose-Escalation cohort will have priority over the Dose-Expansion cohort
- For parallel Dose-Escalation cohorts slot assignment will be completed in an alternating manner
- For parallel Dose-Expansion cohorts below the RP2D, slot assignment will be completed in an alternating manner, taking into account that each cohort aims to have 50% of participants have [redacted]
- In the Dose-Expansion Cohort at the RP2D, participants will be stratified based on histotype/genotype. If more than one mutation is present, participants will be stratified into the genotype with the lowest enrollment.
- Sites may enroll participants into the Dose-Expansion Component if there is no Dose-Escalation Cohort open for enrollment (Appendix 9A)

Participants will be allocated a screening number at the time of signing the informed consent form (ICF). If a participant is a screen failure, the number will not be reassigned.

6.4. Study Intervention Compliance

6.4.1. Compliance Instructions

Dosing instructions will be provided to the participant, and participant compliance with study intervention will be reviewed at each visit. Compliance will be assessed by counting returned capsules (RMC-4630) and tablets (cobimetinib), in conjunction with participant diary information and participant questioning. Since Osimertinib is supplied as part of Standard of Care by local pharmacies, compliance will only be assessed by reviewing participants' diaries and questions asked during clinic visits. Refer to Section 8.4 in the event a participant is suspected to have taken greater than the assigned dosage.

6.4.2. Missed Dose

***RMC-4630*:** If a participant misses a dose, it may be taken at the time the omission was discovered provided that it is within 24 hours of the original administration time. Otherwise, the dose should not be administered and should be recorded as an omission. The participant should not administer more than the recommended dose.

***Cobimetinib*:** If a dose of COTELLIC is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.

RMC-4630 and Cobimetinib: Twice weekly dosing schedule on D1, D2

If a participant misses a D1 dose of either drug, it should be taken as soon as the missed dose is discovered. The D2 dose should then follow 24-hours after. If the participant misses D2 dose, it should be taken as soon as the missed dose is discovered provided there is at least a 24-hour gap between D1 dose and D2 dose. If the gap between D1 and D2 dose is more than 48 hours, D2 dose should not be administered and should be recorded as an omission. The participant should not administer more than the recommended dose.

RMC-4630 Twice weekly dosing schedule on D1, D4 and Osimertinib QD (alternative schedule) (Study in US only)

If a participant misses a dose of RMC-4630, it may be taken at the time the omission was discovered provided that is within 24 hours of the original administration time. Otherwise, the RMC-4630 dose should not be administered and should be recorded as an omission. The participant should not administer more than recommended dose.

If a participant misses a dose of osimertinib, do not make up the missed dose and take the next dose as scheduled

RMC-4630 Twice weekly dosing schedule on D1, D2 and osimertinib QD (Study in US only)

If a participant misses a D1 dose of RMC-4630, it should be taken as soon as the missed dose is discovered. The D2 dose should then follow 24-hours after. If the participant misses D2 dose, it should be taken as soon as the missed dose is discovered provided there is at least a 24-hour gap between D1 dose and D2 dose. If the gap between D1 and D2 dose is more than 48 hours, D2 dose should not be administered and should be recorded as an omission. The participant should not administer more than the recommended dose. If a participant misses a dose of osimertinib, do not make up the missed dose and take the next dose as scheduled.

6.5. Permitted Concomitant Therapy

Supportive care (eg, antiemetics, analgesics, blood transfusions, hematopoietic growth factor support) may be used at the investigator's discretion and in accordance with institutional procedures. Localized radiotherapy used for palliative purposes may be considered after discussion with the Medical Monitor. Anticoagulation with low-dose aspirin, low-molecular weight heparin (LMWH), and direct Factor-Xa inhibitors are allowed. Contraceptives are also allowed throughout the study as described in Section 5.1.

Antacids are permitted but should not be consumed within 3-4 hours before or after RMC-4630 and cobimetinib or RMC-4630 and osimertinib administration.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Route of administration

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Concomitant Therapy

In addition to prohibited medications/foods listed in Exclusion Criteria (Section 5.2), a complete list of prohibited medications during study treatment are provided in this section (Appendix 8).

The following medications are prohibited while on study treatment:

- [redacted]
- [redacted]
- [redacted]
  [redacted]
- [redacted]
- [redacted]
- [redacted]

6.6. Dose Modification

6.6.1. Dose Modification Rules

A 28-day cycle will be maintained, and dose interruption will be noted in the 28-day cycle schedule.

In the Dose-Escalation cohorts, there will be no dose reductions or modifications during C1, 28-day DLT assessment period unless a DLT has occurred. After C1 and in the Dose-Expansion cohorts, if a dose reduction is recommended, then the combination dose level should be the previous lower dose level considered to be tolerable in prior participants receiving that dose. If the previous lower dose level comprised of two parallel cohorts (ie, two combination dose levels), the investigator and sponsor Medical Monitor may choose one of two lower combination dose level based on the participant's medical and study drugs history.

[redacted]

[redacted]

Two types of dose modifications are allowed, "dose interruption" and "dose level reduction." The decision will be per investigator, according to the dose modification criteria and guidelines outlined in Section 6.6. Any allowed dose modification and any deviation from the intended dose (missed doses or overdoses due to participant error) should be documented on the dose electronic Case Report Form (eCRF).

6.6.2. Dose Modification Criteria for RMC-4630 and Cobimetinib

In general, dose adjustments should be based on attribution to a particular drug, if known. Certain adverse events are known to be associated with administration of cobimetinib (cobimetinib IB) whereas others have been observed with the administration of RMC-4630 in clinical or preclinical studies (RMC-4630 IB). [redacted]

The following principles apply to Dose Escalation component of the study and should be employed for Grade 3 and certain Grade 4 AEs.

- If the AE is a known toxicity of cobimetinib only, cobimetinib should be interrupted and then dose reduced one level if recovery to ≤Grade 1 occurs within 28 days. RMC-4630 should be continued at the same dose. However, at the investigator's discretion, RMC-4630 may be held if the AE does not improve with holding cobimetinib. If the AE does not resolve within 28 days from onset, permanently discontinue cobimetinib.
- If the AE is suspected to be due to RMC-4630, RMC-4630 should be interrupted and then dose reduced one level if recovery to ≤Grade 1 occurs within 28 days. Cobimetinib should be continued at the same dose. However, at the investigator's discretion, cobimetinib may be held if the AE does not improve with holding RMC-4630. If the AE does not resolve within 28 days from onset, permanently discontinue RMC-4630.
- If the AE is known for both drugs, hold both drugs until recovery to ≤Grade 1. Restart at a reduced dose of the drug that was last escalated by one dose level if the recovery to Grade <1 is within 28 days. The second drug may also be dose reduced by one level at the investigator's discretion and after discussion with the sponsor Medical Monitor.
- If the AE is unknown for either drug, hold both drugs until recovery to ≤Grade 1. Restart at a reduced the dose of the drug that was last escalated by one dose level if the recovery to grade <1 is within 28 days. The second drug may also be dose reduced by one level at the investigator's discretion and after discussion with the sponsor Medical Monitor.

Dose escalation- If more than 2 dose reductions are required of cobimetinib, then permanently discontinue cobimetinib. RMC-4630 may be continued as monotherapy provided that the participant is benefitting from treatment with no evidence of disease progression. If RMC-4630 is continued as a single agent, please refer to specific guidelines provided at the bottom of this section. If more than 2 dose reductions of RMC-4630 are required, permanently discontinue both drugs.

Final expansion at RP2DS (Refer to Table 11)

- [redacted]
- There are no dose reductions permitted for cobimetinib. If dose reduction for cobimetinib is required, then permanently discontinue cobimetinib.

RMC-4630 may be continued as monotherapy provided that the participant is clinically benefitting from treatment with no evidence of disease progression. [redacted] Guidelines in Table 9 mainly pertain to the dose escalation phase of the study. The investigator or treating physician should use his/her best medical judgement for management.

General guidance for dose modification during final dose expansion is shown in Table 10.

Table 9 Dose Modification Guidelines for RMC-4630 and Cobimetinib

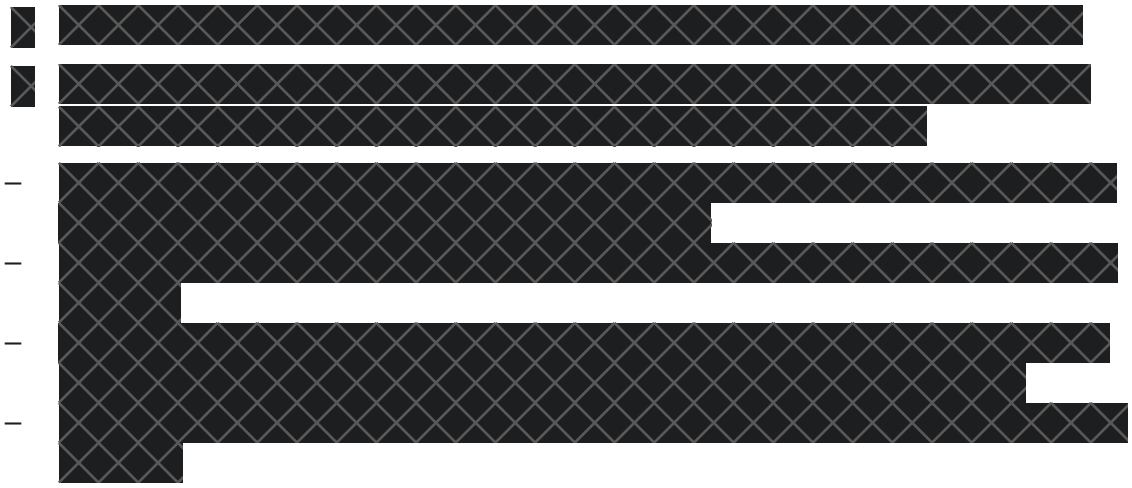
Table 10 Dose Modification Guidelines with RMC-4630 and Cobimetinib During Final Dose Expansion

Severity Grade	Action
Grade 1	Continue both drugs at the current dose
Grade 2	May continue both drugs without dose interruption and manage the toxicity using institutional guidelines. However, depending on the toxicity, dose interruption may be considered for one drug if the toxicity is a known toxicity of RMC-4630 versus cobimetinib. Upon recovery to baseline or Grade 1, re-start treatment at the same dose. If the toxicity re-occurs, consider a dose reduction.
Grade 3-4	

Dose modifications may also occur following the first cycle (DLT assessment period) during the Dose-Escalation Component or Dose-Expansion Component (where applicable) in the following specific instances:

- Any participant who experiences a Grade 3 AE that constitutes a DLT may be considered for dose reduction to last dose cohort upon recovery of the AE to Grade 1 or baseline if deemed medically appropriate by the investigator and Medical Monitor. These participants will be considered to have experienced a DLT at the original dose and, therefore, will not be permitted to remain at the same dose.
    - For participants in the Final Expansion Cohort – if an AE/SAE occurs within the first cycle and meets the DLT definition, participant may dose reduce RMC-4630 to 100 mg D1D2.
- Any participant who experiences a < Grade 3 AE that does not constitute a DLT but that recurs more than once (≥ Grade 2) after recovering from the initial onset of the AE may be considered for a dose reduction upon recovery of the AE to Grade 1 or baseline if deemed medically appropriate by the investigator and sponsor Medical Monitor. Discontinuation of the study medications after third occurrence of the AE that is Grade 2 (intolerable) or Grade 3.
- Re-challenge at the same or lower dose may be considered after resolution of treatment-related or treatment-unrelated AEs provided the AE did not meet DLT criteria. If the AE recurs, dose modification may be considered.
- Continuation of a single agent RMC-4630 may be allowed if there is presence of, or potential for, clinical benefit as assessed by the investigator and sponsor Medical Monitor. The dose and schedule of RMC-4630 may be cross-referenced to the on-going monotherapy study RMC-4630-01. The options are:

Dose Escalation:



Final Expansion at RP2DS:

[redacted]

Table 11 RMC-4630 and Cobimetinib Dose Levels (Final Expansion at RP2DS)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6.6.3. Dose Modification Criteria for RMC-4630 and Osimertinib (Study in US Only)

In general, dose adjustments should be based on attribution to a particular drug, if known.

[redacted]

- [redacted]

[redacted]

[redacted]

If more than 1 dose reduction is required of osimertinib, then permanently discontinue osimertinib (please see Table 12). RMC-4630 may be continued as monotherapy provided that the participant is benefiting from treatment with no evidence of disease progression (Table 13). If more than 2 dose reductions of RMC-4630 are required, permanently discontinue both drugs.

Table 12 Osimertinib Dose Levels

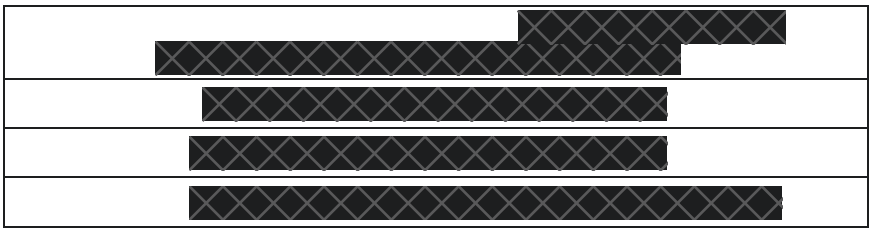
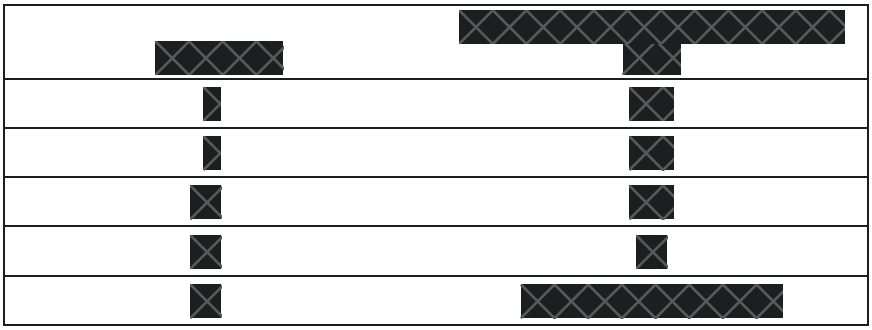


Table 13 RMC-4630 Dose Levels (Dose Escalation)



Actual dose levels during dose escalation may be different as intermediate dose levels of RMC could be explored per Dose Committee decision.

General guidance and dose modification guidelines for a subset of common AEs seen with osimertinib or other inhibitors of the RAS-MAPK pathway are shown in Table 14 below. The investigator or treating physician should use his/her best medical judgement for management.

Table 14 Dose Modification Guidelines for RMC-4630 and Osimertinib

AE	Action
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE	Action
Dose Modification Guidelines for RMC-4630 and Osimertinib (cont.)	
[redacted]	[redacted]
[redacted]	[redacted]

Dose modifications may occur at any time during the study with following specific instances:

- During DLT assessment period of the Dose-Escalation Component, dose level reduction is not allowed unless participant has already experienced a DLT.
- Any participant who experiences a Grade 3 AE that constitutes a DLT may be considered for dose reduction to last dose cohort upon recovery of the AE to Grade 1 or baseline if deemed medically appropriate by the investigator and Medical Monitor. These participants will be considered to have experienced a DLT at the original dose and, therefore, will not be permitted to remain at the same dose. The starting dose level for RMC-4630 for osimertinib combination arm is 140 mg D1D2. [redacted]
- Any participant who experiences a < Grade 3 AE that does not constitute a DLT but that recurs more than once (≥ Grade 2) after recovering from the initial onset of the AE may be considered for a dose reduction upon recovery of the AE to Grade 1 or baseline if deemed medically appropriate by the investigator and sponsor Medical Monitor.
- Any participant who requires a dose interruption of >4 doses for RMC-4630 or >14 doses for osimertinib due to a treatment-related AE Grade < 3 may be considered for a dose reduction. Participants in the DLT window will be considered to have experienced a DLT

at the original dose and schedule and, therefore, will not be permitted to remain at the same dose and schedule.

- Re-challenge at the same or lower dose may be considered after resolution of treatment-related or treatment-unrelated AEs provided the AE did not meet DLT criteria. If the AE recurs, dose modification may be considered.
- If both drugs have been on hold for a treatment related AE, a staggered re-challenge strategy may be considered by re-starting either RMC-4630 or osimertinib first followed by the second agent a week later. This strategy might minimize the risk of recurrence of the AE which led to dose interruption and may help understand which drug may be driving the toxicity.
- Continuation of RMC-4630 alone may be allowed if there is presence of clinical benefit as assessed by the investigator and sponsor Medical Monitor.

6.6.4. Supportive Care Guidelines for Selected Expected Toxicities

Please refer to Table 9 for dose modification guidelines for RMC-4630 and cobimetinib or Table 14 for RMC-4630 and osimertinib. [redacted] The investigator or treating physician should use his/her best medical judgement for management. Published guidelines are available for MEK, BRAF and RTK inhibitors (Califano 2015, Welch 2015, Daud 2017) and guidelines for selected toxicities are summarized below.

6.6.4.1. [redacted]

[redacted]

[redacted]

6.6.4.2. [redacted]

[redacted]

6.6.4.3. [redacted]

[redacted]

[redacted]

[redacted]

6.6.4.4. [redacted]

[redacted]

6.6.4.5. [redacted]

[redacted]

6.6.4.6. [redacted]

[redacted]

6.6.4.7. [redacted]

[redacted]

6.6.4.8. [redacted]

[redacted]

6.6.4.9. [redacted]

[redacted]

6.6.4.10. [redacted]

[redacted]

6.6.4.11. [redacted]

[redacted]

6.6.4.12. [redacted]

[redacted]

6.6.4.13. [redacted]

[redacted]

6.7. Intervention after the End of the Study

Participants who continue to receive study intervention at the end of the study and are considered to be deriving clinical benefit from RMC-4630 and cobimetinib or RMC-4630 and osimertinib will be considered for enrollment in a separate extended use or roll-over study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention. Refer to the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

Participants may stop study therapy yet continue to be monitored in the study under the following circumstances:

- A participant who experiences a Grade 4 AE, including those that meet the criteria of a DLT (ie, during C1), but is deemed by the investigator not to meet the criteria for withdrawal from the study (Section 7.2).
- Prolonged QTcF (defined as QTc using Fridericia's formula [QTcF] >500 msec **OR** change from baseline of QTcF >60 msec) and that does not resolve after excluding other causes

A participant must be discontinued from protocol-prescribed therapy and removed from the study if any of the following apply:

- Documented disease progression based on RECIST v1.1
  - In certain circumstances (eg, an isolated site of progression with responses at other sites that may be amenable to localized radiotherapy), participants may be allowed to continue therapy during and after radiation with approval from sponsor Medical Monitor.
- Significant adverse events leading to discontinuation of study medications (report on adverse event eCRF) (Section 6.6)
- Death
- Participant’s request to withdraw from study treatment or withdraw consent
- Ineligibility
- Unwillingness or inability to comply with study requirements
- Initiation of alternative anticancer therapy
- Investigator’s decision
  - Clinical need for concomitant or other ancillary therapy that is not permitted in the study
  - Unrelated intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree

  - Investigator believes that it is in the best interest of the participant to withdraw from the study
- Pregnancy
- Lost to follow-up
- Sponsor's decision to terminate the study

Participants who have stable disease as best response will be allowed to continue on treatment provided the investigator believes it is in the participant's best interest and none of the above criteria have been met.

Participants who discontinue study treatment should complete the safety follow-up or EOT visit, within 30 days after the last treatment dose. Participants who do not withdraw consent will also undergo long-term follow-up until death or end of study or lost to follow-up. See Section 7.2 for details on study discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant may be withdrawn from the study for any of the following reasons:

- Participant's withdrawal of consent for participation in the study
- Sponsor's decision to terminate the study
- Participant is lost to follow-up
- Death

If study discontinuation occurs at the same time as treatment discontinuation, every effort should be made to complete the safety follow-up or EOT visit, within 30 days after the last treatment dose. Participants who do not withdraw consent will also undergo a long-term follow-up for survival (SoA in Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request in writing destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- The maximum amount of blood collected from each participant over a 12-cycle duration of the study, including any extra assessments that may be required, will not exceed 0.9 L. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Participants will be assessed for response using RECIST v1.1 (Appendix 6) as assessed by the investigator. All measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Measurable disease is not required in the Dose-Escalation Component; however, disease must be evaluable by other measures and documented accordingly. Response assessments will be assessed by the investigator based on physical examination (including measurement of cutaneous lesions) and CT scans or MRI. Imaging should include chest and abdomen (neck and pelvis are to be included depending on primary tumor type and investigator assessment). At the investigator's discretion, the imaging studies may be repeated at any time if disease progression is suspected. Additional studies, such as positron emission tomography (PET) scans, should be performed if clinically indicated. Care should be taken to repeat the same modality used at screening throughout the study and to ensure all anatomy imaged at screening is again imaged at follow-up scans for any given participant. As part of the tumor assessment, physical examinations should include all areas of tumor involvement that are amenable to examination, including biopsy sites, lymph nodes, and bone tenderness, if applicable.

All imaging studies should be evaluated by a local radiologist with expertise in the imaging modality. The investigator is responsible for determining the overall response at each timepoint.

The first response assessment will occur after completion of C2 (C3D1 ± 7 days). Subsequent response assessments will occur every 2 cycles through the end of C6 (C7D1 ± 7 days) and then every 3 cycles.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat (HEENT), dermatologic, cardiovascular, respiratory, GI, lymphatic, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded. A symptom/AE-directed physical examination should be performed as indicated by participant presentation or participant reported symptoms.

- A limited examination should include an evaluation of the HEENT, dermatologic, cardiovascular, respiratory, and GI systems. A symptom/AE-directed physical examination should be performed as indicated by participant presentation or participant reported symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

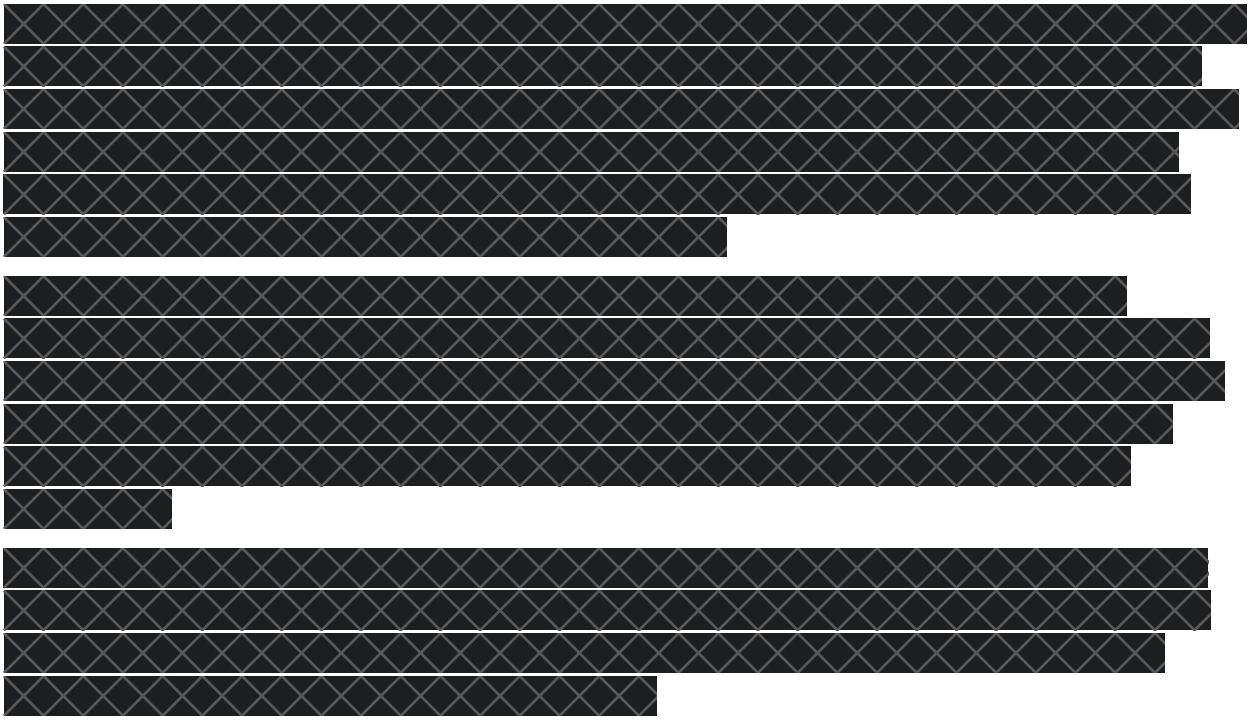
8.2.2. Vital Signs

Vital signs will be measured, preferably in a seated position, after approximately 5-minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and pulse oximetry. Results should be recorded on the appropriate eCRF.

8.2.3. Weight and Height

Weight should be measured throughout the study as indicated in the SoA. Coats and shoes should be removed prior to measurement. Height should be measured at baseline, preferably without shoes.

8.2.4. Electrocardiograms



8.2.5. Echocardiograms/Multigated Acquisition Scans

[redacted]

8.2.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified where possible, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.
    - If laboratory values from non–protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are

considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the eCRF.

8.2.7. [redacted]

[redacted]

8.2.8. [redacted]

[redacted]

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention(s) (Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Monitoring and recording of AEs and SAEs will be conducted throughout the study. After the signing of the ICF, but prior to initiation of study intervention, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures, such as biopsies or medication washout). Any medical occurrence that begins before the start of study intervention but after obtaining informed consent, and which is not considered an SAE caused by a protocol-mandated intervention, will be recorded on the Medical History/Current Medical Conditions Section of the eCRF not the AE section.

All AEs and SAEs will be collected from the start of intervention until the safety visit or EOT visit, whichever is later. Any SAE that is determined to be study-drug related (possibly, probably, or definitely related) will be followed to resolution or stabilization, is determined to be irreversible by the investigator, the participant is lost to follow-up, or it has been determined that the study treatment is not the cause of the AE/SAE, whichever occurs first. After this period,

investigators should report only SAEs that are thought to be related to RMC-4630, RMC-4630 and cobimetinib combination, or RMC-4630 and osimertinib combination. AE/SAE reporting will end after the participant initiates alternative cancer treatment.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of investigator awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts through the last study visit. All AEs (regardless of relationship to study intervention) and SAEs determined not to be study intervention related (ie, not related and unlikely related) will be followed through the last study visit and be noted as “continuing” if not resolved at this visit.

All SAEs considered study-drug related will be followed until resolution, stabilization, is determined to be irreversible by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or it has been determined that the study treatment is not the cause of the AE/SAE, whichever occurs first. AE/SAE reporting will end after the participant initiates alternative cancer treatment.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification (eg, 24 hours of becoming aware of the event) by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until EOT visit.
- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Safety Committees

Two safety committees will be employed during this study: the Dose Committee and the ISMC.

The Dose Committee, composed of Sponsor representatives and investigators, will evaluate the C1 safety data after the 28-day DLT window once the third participant in each dose cohort has completed. This committee will make the final decision on dosing for the next cohort, taking in to account all available safety data including any available data on any fourth participant enrolled in a dose cohort, if applicable (Section 4.1.1.1). In addition, all available efficacy, safety, and PK/PD data will be used to determine whether Dose-Expansion may commence at the end of each Dose-Escalation Cohort.

In addition to the safety data reviews for dose escalation and cohort expansion, the ISMC will review emergent safety data from the RMC-4630 program after approximately every 3 months or after the first 6 participants have completed 2 cycles, whichever is earlier. Subsequently the committee will review data approximately every 3 months. The committee may adjust the timing of the review from the defined schedule, depending on the rate of enrollment. The committee will consist of the Medical Monitor, Drug Safety Monitor, and a Biostatistician. Relevant findings from the safety data reviews will be discussed with the study investigators. Based on the ongoing safety assessments, the committee may recommend changes in dosing regimen or other alterations to study procedures. The Medical Monitor or Drug Safety Monitor may convene a meeting sooner should any concerns arise from review of data or from the investigators.

8.4. Treatment of Overdose

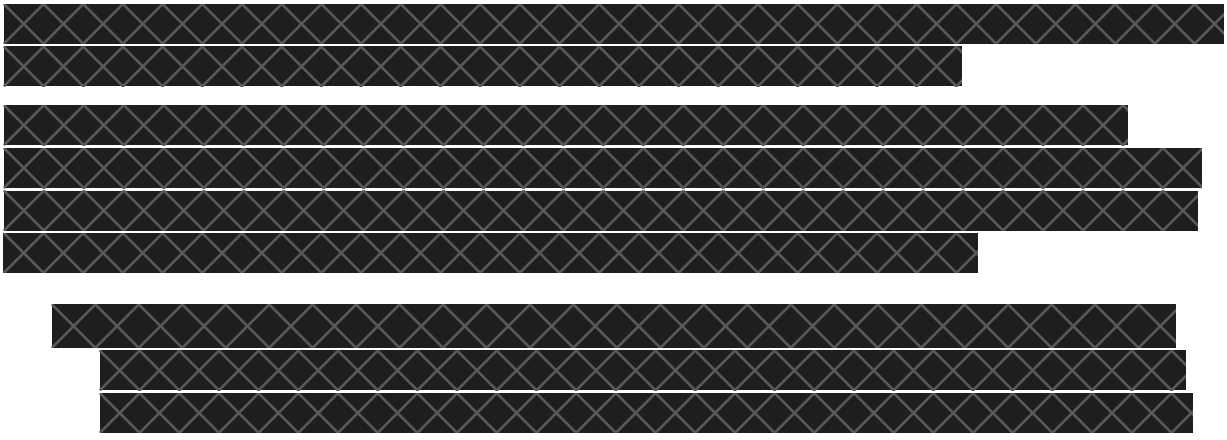
For this study, any dose of RMC-4630, cobimetinib, or osimertinib, 1.5× greater than the intended dose per administration or 2 administrations at the intended dose or more within <12 hours for QD dosing or < 24 hours for intermittent dosing will be considered an overdose. Similarly, for twice weekly D1, D2 dosing schedule, 2 administrations of the same agent <12 hours apart will be considered an overdose. There is no clinical experience with an overdose of RMC-4630, cobimetinib, or osimertinib in human clinical trials. No experiments have been performed to determine whether the effects of an overdose can be reversed, and there are no known antidotes.

Revolution Medicines does not recommend specific treatment for an overdose. The individual should be monitored clinically, and supportive care should be undertaken as clinically indicated.

In the event of an overdose, the investigator should:

1. Halt the dispension and administration of the involved medication. The investigator may also hold the second medication based on his/her clinical judgement.
2. Contact the Medical Monitor immediately.
3. Closely monitor the participant for any AE/SAE, ECG, and laboratory abnormalities (blood glucose, liver function tests, creatinine, blood urea nitrogen (BUN), CPK, and complete blood count) until RMC-4630 and/or cobimetinib can no longer be detected systemically.
4. Obtain a plasma sample for PK analysis within 1 to 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document the quantity as well as the duration of the overdose in the eCRF.
6. Decisions regarding resumption of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.6. Pharmacodynamics

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.8. Other Biomarkers

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.9. Health Economics and Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This is a 2-arm, Phase 1b/2 dose-escalation study designed to assess safety, to define an MTD and a recommended dose and regimen for a phase 2 study, and to obtain a preliminary assessment of efficacy of RMC-4630 in combination with cobimetinib in 1 arm and RMC-4630 in combination with osimertinib in the 2nd arm in adult participants with relapsed/refractory solid tumors. The emphasis will be on safety evaluation and any efficacy analyses will be an estimation of the treatment effect. Descriptive statistics will be used to summarize baseline demographic and disease characteristics, treatment administration, efficacy and safety outcomes, as well as PK and PD outcomes.

Descriptive summaries of discrete data will present the number of study participants and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size.

9.1. Statistical Hypotheses

There are no formal hypotheses to be tested in this study.

9.2. Sample Size Determination

Both arms of the study will include two components: a Dose-Escalation Component and a Dose-Expansion Component consisting of 6 genotypic/histotypic cohorts.

Doses for both RMC-4630 and cobimetinib will vary in dose escalation component of arm 1. Dose escalation recommendations will be conducted using a CRM model for RMC-4630 and cobimetinib arm (Appendix 10). Table 1 illustrates sample size estimation based on “Scenario 1” depicted in Figure 2. The study is expected to enroll approximately 144 participants as follows:

- Up to 42 participants during the Dose-Escalation Component, assumes 7 total combination dose cohorts (RMC-4630 dosed twice weekly on D1, D4 or D1, D2 with cobimetinib dosed once daily on 21/7 schedule; RMC-4630 and cobimetinib dosed twice weekly on D1, D2) with 3 to 6 participants per dose. The MTD cohort will enroll at least 6 participants.
- After reaching threshold of activity and achieving DLT clearance at a dose level, at least 24 additional participants may be enrolled during expansion prior to RP2D for a maximum 12 participants per dose level (assumes 4 combination dose expansion cohorts).

- Up to 90 participants (15 per class of mutation x 6 strata) will be enrolled at RP2D (combination dose level 4a). Assuming 12 participants are already enrolled during dose escalation and expansion into cohort that will be declared RP2D, additional 78 participants will be enrolled into RP2D cohort.

The primary objective of this study is safety evaluation. The objective the efficacy evaluation is to generate data which will enable a preliminary estimation of the treatment effect. The treatment effect will be interpreted in the clinical context of specific genotypes and histotypes. The target disease stabilization rate is 30%. If 5 out of 15 participants have achieved disease stabilization, the observed disease stabilization rate would be 33% where the lower limit of the 95% CI is 12%, which excludes a null rate of 10%. A sample size of 15 will provide preliminary evidence of efficacy of RMC-4630 and cobimetinib. Replacement of efficacy unevaluable participants at RP2D may be considered.

With a sample size of 144 study participants, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 76%, 95%, or >99%, respectively.

Only dose for RMC-4630 may vary in dose escalation component of arm 2, while dose of osimertinib will remain constant at 80 mg once daily. Dose escalation/de-escalation recommendations will be following mTPI-2 design for RMC-4630 and osimertinib arm.

- Up to 18 participants during the Dose-Escalation Component, assumes up to 3 total combination dose cohorts with maximum of 6 participants per dose cohort. The MTD cohort will enroll at least 6 participants.
- After reaching threshold of activity and achieving DLT clearance at a dose level, 6-18 participants may be enrolled in the dose expansion cohort for a total of 24 participant in RMC-4630 and osimertinib arm 2 of the study.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 15.

Table 15 Population Definitions

Population	Description
Enrolled	All participants who sign an ICF and meet eligibility criteria
Treated	All participants who take at least 1 dose of study intervention
Evaluable	Evaluable for DLT: All participants in the treated population who have completed the DLT period or who have discontinued due to AEs or death (unless relationship to RMC-4630 and cobimetinib can be ruled out) prior to the end of the DLT period. In addition, participants must receive at least 75% of planned dose (not miss ≥ 3 doses of RMC-4630 and cobimetinib on D1D2 intermittent schedule and ≥ 6 doses of cobimetinib on 21 on/7 off schedule, and ≥ 8 doses of osimertinib within the DLT window for reasons other than toxicity). This population will be the primary population for fitting the dose-toxicity model. Evaluable for efficacy: All participants with measurable disease at baseline, who take at least 1 dose of study intervention and underwent one post-baseline response assessment or who die or had clinical progression prior to first post-baseline response assessment
Safety	All participants who take at least 1 dose of study intervention

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; ICF, informed consent form.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. The full details of the escalation and expansion rules, including prior distributions for the dose-toxicity model, simulations, and operating characteristics, will be documented in separate statistical simulation report.

9.4.1. Efficacy Analyses

The statistical analysis methods to be used during the efficacy analyses by endpoint is presented in Table 16.

Table 16 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	ORR is defined as the proportion of participants who achieve a CR or PR per RECIST v1.1. ORR and the corresponding 95% two-sided confidence interval will be derived. DOR is defined as the interval from the first documentation of CR or PR to the earlier of first documentation of definitive disease progression or death due to any cause, whichever occurs first. Participants who are still alive and free from progression at the time of data cutoff date, are lost to follow-up, have discontinued from the study, or have initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. The Kaplan-Meier method will be used to estimate PFS and DOR curves and corresponding quartiles. Kaplan-Meier median will be calculated with a 2-sided 95% confidence interval. Pharmacokinetics assessed by noncompartmental methods and summarized by descriptive statistics (mean or geometric mean, standard deviation, coefficient of variation, minimum, and maximum).
Exploratory	Will be described in the statistical analysis plan finalized before database lock. Absolute and percentage changes of pharmacodynamic assessments at baseline and during treatment.

Abbreviations: CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; RAS-MAPK, RAS-mitogen-activated protein kinase; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1.

The secondary efficacy endpoints of ORR and DOR will be summarized for participants enrolled at the RP2D. If available, genotyping results from the central laboratory will supersede those from local tests for primary and secondary endpoints. Local results may be included in exploratory analyses.

PK parameter estimates, including but not limiting to the ones listed below, will be determined when possible for RMC-4630 and cobimetinib:

- C_{max} (observed)
- T_{max} (observed)
- AUC_{0-t} and AUC_{inf}
- $t_{1/2}$
- Accumulation ratio

Unless otherwise specified, the PK parameters will be estimated based on noncompartmental analysis methods. These estimates will be summarized descriptively by dose cohort. All PK parameters will be computed using actual elapsed time calculated relative to dose administration.

Dose proportionality across dose levels will be characterized by plotting C_{max} and AUC versus dose. Exploratory analyses may be performed to evaluate the relationship between the estimated PK parameters and PDs, selected safety, biomarker, or clinical effect endpoints.

The PK and PD analyses will be presented in a separate report that may be integrated into the main clinical study report.

9.4.2. Safety Analyses

All DLT modeling will be performed on the DLT-evaluable population. All other safety analyses will be performed on the Safety Population. The statistical analysis methods to be used during the safety analyses by endpoint is presented in Table 17.

Table 17 Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Summaries of AEs, SAEs, and AEs leading to treatment discontinuation and dose modification, changes in laboratory test results and changes in vital signs, and DLT rate
Secondary	Not applicable
Exploratory	Will be described in the statistical analysis plan finalized before database lock

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event.

AEs and SAEs will be displayed by combination dose level.

9.4.3. Other Analyses

Additional efficacy and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock.

9.5. Interim Analyses

No formal interim analysis will be conducted. However, as this is an open-label study with regular determinations of dosing levels, several analyses may be conducted at specific points during the study as well as at the end of the study. The Sponsor reserves the right to report interim data after discussion with the principal investigators.

10. REFERENCES

Bollag G, Tsai J, Zhang J, et al. Vemurafenib: the first drug approved for *BRAF*-mutant cancer. *Nat Rev Drug Discov*. 2012;11(11):873-86. doi:10.1038/nrd3847.

Brown AP. Development of serum calcium and phosphorus as clinical biomarkers for drug-induced systemic mineralization: case study with a MEK inhibitor. In: Bleavins MR, Carini C, Jurima-Romet M, and Rahbari R, editors. *Biomarkers in Drug Development: A Handbook of Practice, Application, and Strategy*. Hoboken, NJ. John Wiley & Sons; 2010. p. 301–22.

Califano R, Tariq N, Compton S, Fitzgerald DA, et al. Expert Consensus on the Management of Adverse Events. Drugs. 2015;75(12):1335-1348. doi:10.1007/s40265-015-0434-6

Caunt CJ, Sale MJ, Smith PF, et al. MEK1 and MEK2 inhibitors and cancer therapy: the long and winding road. *Nat Rev Cancer*. 2015; 15:577-592. doi:10.1038/nrc4000.

Chen YN, LaMarche MJ, Chan HM, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. *Nature*. 2016;535(7610):148-52. doi:10.1038/nature18621.

Cheng Y, Tian H. Current Development Status of MEK Inhibitors. Molecules. 2017;22(1551):1-20.

Dardaei L, Wang HQ, Singh M, et al. SHP2 inhibition restores sensitivity in ALK-rearranged non-small-cell lung cancer resistant to ALK inhibitors. 2018. *Nature Medicine*. doi:10.1038/nm.4497.

Daud A and Tsai K. Management of Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma. *The Oncologist*. 2017;22(7):823-833. doi:10.1634/theoncologist.2016-0456.

DeGeorge JJ, Ahn CH, Andrews PA, et al. Regulatory considerations for nonclinical development of anticancer drugs. *Cancer Chemother Pharmacol*. 1997;41(3):173-85. doi:10.1007/s002800050726.

De La Cruz-Merino, Luis, et al. "Clinical features of serous retinopathy observed with cobimetinib in patients with BRAF-mutated melanoma treated in the randomized coBRIM study." Journal of translational medicine 15.1 (2017):146.

Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signaling pathways in cancer. *Oncogene*. 2007;26(22):3279-90. doi:10.1038/sj.onc.121042.

Duncan KE, Chang LY, Patronas M. "MEK inhibitors: a new class of chemotherapeutic agents with ocular toxicity." Eye 29.8 (2015):1003-1012.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45(2):228-247. Doi:10.1016/j.ejca.2008.10.026.

Fedele C, Ran H, Diskin B, et al. SHP2 inhibition prevents adaptive resistance to MEK inhibitors in multiple cancer models. *Cancer Discov*. 2018;8 (10) 1237-1249. doi:10.1158/2159-8290.

Han K, Jin JY, Marchand M, et al. Population pharmacokinetics and dosing implications for cobimetinib in patients with solid tumors. *Cancer Chemother Pharmacol.* 2015:76:917-924. doi:10.1007/s00280-015-2862-0.

Heuchel R, Berg A, Tallquist M, et al. Platelet derived growth factor ß receptor regulates interstitial fluid homeostasis through phosphatidylinositol-3' kinase signaling. Proc Natl Acad Sci USA. 1999;96 : 11410-11415. doi:10.1073/pnas.96.20.11410

Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: Correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol*. 2003;21:3798-807. doi:10.1200/JCO.2003.11.069.

Hui E, Cheung J, Zhu J, et al. T cell costimulatory receptor CD28 is a primary target for PD-1−mediated inhibition. *Science*. 2017;355(6332):1428-33. doi:10.1126/science. aaf1292

Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in *NF1* and RASopathy genes in sun-exposed melanomas. *Nat Genet*. 2015;47(9):996-1002. doi:10.1038/ng.3361

Larkin J, Ascierto P, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867-1876. doi:10.1056/NEJMoa1408868

Lee L, Niu H, Rueger R, et al. The safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of CH4987655 in healthy volunteers: target suppression using a biomarker. *Clin Cancer Res.* 2009;15(23):7368-74. doi:10.1158/1078-0432.CCR-09-1696

Lito P, Solomon M, Li LS, Hansen R, Rosen N. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. *Science*. 2016;351(6273):604-8. doi:10.1126/science.aad6204

Liu F, Yang X, Geng M, et al. Targeting ERK, an Achilles' Heel of the MAPK pathway, in cancer therapy. *Acta Pharm Sinica B* 2018;8(4):552-562. doi:10.1016/j/apsb.2018.01.008

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

Lu H, Chen L, Velazquez R, et al. SHP2 inhibition overcomes RTK-mediated pathway re-activation in KRAS mutant tumors treated with MEK inhibitors. Mol Cancer Ther. 2019;19(7):1323-1334. doi:10.1158/1535-7163.MCT-18-0852

Mainardi S, Mulero-Sanchez A, Prahallad A, et al. SHP2 is required for growth of KRAS-mutant non-small-cell lung cancer in vivo. *Nat Med.* 2018;24(7):961-967.

Mazharian A, Mori J, Wang Y, et al. Megakaryocyte-specific deletion of the protein-tyrosine phosphatases Shpl and Shp2 causes abnormal megakaryocyte development, platelet production, and function. *Blood*. 2013 :121(20):4205-4219. doi:10.1182/blood-2012-08-449272

Méndez-Martínez S, et al. "Ocular adverse events associated with MEK inhibitors." Retina 39.8 (2019):1435-1450.

Nichols RJ, Haderk F, Stahlhut C, et al. Efficacy of SHP2 phosphate inhibition in cancers with nucleotide-cycling oncogenic RAS, RAS-GTP dependent oncogenic BRAF and NF1 loss. bioRxiv. 2017. doi:10.1101/188730

Nichols RJ, Haderk F, Stahlhut C, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. *Nature Cell Biology*. 2018;20(9):1064-1073. doi:10.1038/s41556-018-0169-1

Niihori T, Aoki Y, Ohashi H, et al. Functional analysis of PTPN11/SHP-2 mutants identified in Noonan syndrome and childhood leukemia. *J Hum Genet*. 2005;50(4):192-202. doi:10.1007/s10038-005-0239-7

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *P Natl Acad Sci USA*. 2001;98(24):13866-13871. doi:10.1073/pnas.231486598

Ostrem JM, Peters U, Sos M, Wells J, Shokat K. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548-551. doi:10.1038/nature12796

Patricelli MP, Janes MR, Li LS, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. *Cancer Discov*. 2016;6(3):316-329. doi:10.1158/2159-8290.CD-15-1105

Peled M, Tocheva AS, Sandigursky S, et al. Affinity purification mass spectrometry analysis of PD-1 uncovers SAP as a new checkpoint inhibitor. *P Natl Acad Sci USA*. 2018;115(3):E468-E477. doi:10.1073/pnas.1710437115

Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-38. doi:10.1056/NEJMoa1704795

Pietras K, Ostman A, Sjoquist M et al. Inhibition of platelet-derived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. Cancer Research. 2001;61:2929-2934.

Planchard D, Loriot Y, Andre F, et al. EGFR-independent mechanisms of acquired resistance to AZD9291 in EGFR T790M-positive NSCLC patients. Ann Oncol. 2015;26(10):2073-8. doi:10.1093/annonc/mdv319.

Prahallad A, Heynen GJ, Germano G, et al. PTPN11 is a central node in intrinsic and acquired resistance to targeted cancer drugs. *Cell Rep*. 2015;12(12):1978-85. doi:10.1016/j.celrep.2015.08.037

Redig AJ, Capelletti M, Dahlberg SE, et al. Clinical and molecular characteristics of *NF1*-mutant lung cancer. *Clin Cancer Res*. 2016;22(13):3148-56. doi:10.1158/1078-0432.CCR-15-2377

Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced $BRAF^{V600}$-mutated melanoma: a phase 1b study. *Lancet Oncol* 2014;15(9):954-965. doi:10.1016/S1470-2045(14)70301-8.

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.

Ruess DA, Heynen GJ, Ciecielski KJ, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. *Nat Med*. 2018;24(7):954-960.

Shapiro GI, LoRusso P, Kwak E, et al. Phase Ib study of the MEK inhibitor Cobimetinib (GDC-0973) in combination with the PI3K inhibitor pictilisib (GDC-0941) in patients with advanced solid tumors. *Invest New Drugs*. 24 Apr 2019. doi.org/10.1007/s10637-019-00776-6

Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ. FEBS Lett. 2004;574(1-3):37-41. doi:10.1016/j.febslet.2004.07.083

Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med* 2018;378(2):113-125. doi:10.1056/NEJMoa1713137

Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. *Ann Oncol*. 2016;27(6):998-1005. doi:1093/annonc/mdw100

Tartaglia M, Gelb BD. Germ-line and somatic *PTPN11* mutations in human disease. *Eur J Med Genet*. 2005;48(2):81-96. doi:10.1016/j.ejmg.2005.03.001

TGCA – The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543-50. doi:10.1038/nature13385

Tricker EM, Xu C, Uddin S, Capelletti M, et al. Combined EGFR/MEK Inhibition Prevents the Emergence of Resistance in EGFR-Mutant Lung Cancer. *Cancer Discov*. 2015;5(9):960-971. doi:10.1158/2159-8290.CD-15-0063

Tyagi, Pallavi, and Cynthia Santiago. "New features in MEK retinopathy." BMC ophthalmology 18.1 (2018):1-6.

United States Food and Drug Administration. *Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*. FDA, Rockville, MD. 2010. https://www.fda.gov/downloads/Drugs/Guidances/ucm085389.pdf

Wagle M, Kirouac D, Klijn C, Liu B, Mahajan S, et al. A transcriptional MAPK Pathway Activity Score (MPAS) is a clinically relevant biomarker in multiple cancer types. Precision Onco. 2018;2(1):7 doi:10.1038/s41698-018-0051-4

Wang Y et al. Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. *Ther Adv Med Oncol*. 2012 Jan; 4(1): 19-29

Weber ML et al. "Subretinal fluid associated with MEK inhibitor use in the treatment of systemic cancer." JAMA ophthalmology 134.8 (2016):855-862.

Welch SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol.* 2015;7(2):122-36. doi:10.1177/1758834014566428

Wong GS, Zhou J, Liu JB, et al. Targeting wild-type KRAS-amplified gastroesophageal cancer through combined MEK and SHP2 inhibition. Nat Med. 2018;24(7):968-977. doi:10.1038/s41591-018-0022-x

Yang JC-H, Wu Y-L, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, Phase 3 trials. Lancet Oncol 2015;16:141-151. doi:10.1016/S1470-2045(14)71173-8

Yokosuka T, Takamatsu M, Kobayashi-Imanishi W, et al. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. *J Exp Med*. 2012;209(6):1201-17. doi:10.1084/jem.20112741

APPENDIX 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, patient information, advertisements) must be submitted to an Institutional Review Board (IRB) by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of serious adverse events or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

- The investigator or his/her designated representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Per IRB requirements, participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are re-screened are not required to be re-consented; all re-screening should occur within 5 days of the initial date of the screen failure (Section 5.4)

The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Any remaining mandatory samples may be used for optional exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

DATA PROTECTION

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

DISSEMINATION OF CLINICAL STUDY DATA

- The posting of company-Sponsored clinical trial information and tabular study results on the US National Institute of Health (NIH) website (www.clinicaltrials.gov) and on other regional clinical trial registries in countries or regions where the clinical trial is conducted, will comply with local regulations.
- Periodic safety reports will be submitted as required by regulation in the countries where the study is conducted.

DATA QUALITY ASSURANCE

- All participant data relating to the study will be recorded on electronic Case Report Form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved fur such indication, until 2 years after the investigation is discontinued and US Food and Drug Administration (FDA) is notified (ie, in accordance with 21 CFR 312.62(c), unless local regulations or institutional policies require a longer retention period). No records may be

destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

STUDY AND SITE CLOSURE

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

PUBLICATION POLICY

- The Sponsor will comply with the requirements for publication of study results, and the results of this study may be published or presented at scientific meetings. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. The coordinating investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2 CLINICAL LABORATORY TESTS

- The tests detailed in Table A2-1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing: Refer to Section 5.1 for screening criteria, Appendix 4 for women of childbearing potential (WOCBP) criteria, and SoA (Section 1.3) for timepoints.
- The results of each test must be entered into the electronic Case Report Form (eCRF).
- Investigators must document their review of each laboratory safety report.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CPK, creatine phosphokinase; hCG, human chorionic gonadotropin; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; IRB, institutional review board; INR, international normalized ratio; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PTT, partial thromboplastin time; RBC, red blood cell; SAE, serious adverse event; ULN, upper limit of normal; WBC, white blood cell.

[a] Concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case). All events with the defined biochemical abnormalities must be reported as an SAE; and study medications should be permanently discontinued.

[b] See Appendix 4.

[c] Local urine testing will be standard for the protocol unless blood testing is required by local regulation or IRB. For screening, a blood test is required.

APPENDIX 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF ADVERSE EVENT (AE)

Adverse Event (AE) Definition
• An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events (AEs). If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include other invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or INR >1.5 may indicate severe drug-induced liver injury (possible Hy's law case). All qualifying events must be reported as an SAE.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE Recording

- When an adverse event (AE)/serious adverse event (SAE) occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the electronic Case Report Form (eCRF). Additionally, investigative sites should report SAEs within 24 hours of becoming aware of the event to the Chiltern/Covance Pharmacovigilance Department using the paper SAE report form. See section below on the Reporting of SAEs.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the AE/SAE CRF.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity (severity) for each AE and SAE reported during the study using the definitions found in the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 (NCI CTCAE v5) or later. The NCI CTCAE v5 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a participant experience any AE not listed in the NCI CTCAE v5, the following grading system should be used to assess severity:

- Grade 1 (Mild) – experiences which are usually transient, requiring no special treatment, and not interfering with the participant's daily activities
- Grade 2 (Moderate) – experiences which introduce some level of inconvenience or concern to the participant, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe) – experiences which are unacceptable or intolerable, significantly interrupt the participant's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening) – experiences which cause the participant to be in danger of life-threatening consequences and urgent intervention is required
- Grade 5 (Death) – experiences which result in participant death

An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between both study interventions/study drugs and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to Covance Pharmacovigilance Department within 24 hours of receipt of the information on an updated SAE report form to either the email or fax listed below.

REPORTING OF SAES

SAE Reporting to the Sponsor or Designee via Paper CRF

- Investigative sites should report SAEs within 24 hours of becoming aware of the event to the Chiltern/Covance Pharmacovigilance department using the paper SAE report form and any supporting documentation either by email or fax.

  Email: SAEIntake@covance.com

  Fax: 1 888 887 8097
- In rare circumstances and in the absence of email or facsimile equipment, notification by telephone to the Medical Monitor is acceptable with a copy of the SAE report form sent by overnight mail or courier service to Chiltern/Covance CRO Pharmacovigilance Department.
- Contacts for SAE reporting can be found in the Regulatory binder.

APPENDIX 4 CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.
    - Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods [b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods [b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation [c] • oral • injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are NOT acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Hormonal contraception efficacy may potentially be decreased due to interaction with RMC-4630 thus male condoms must be used in addition to hormonal contraception.

COLLECTION OF PREGNANCY INFORMATION

Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive RMC-4630 and cobimetinib under this protocol.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

APPENDIX 6 RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST V1.1)

For this study, response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumours guideline version 1.1 (RECIST v1.1; Eisenhauer 2009).

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows.

a. Measurable Tumor Lesions

Tumor Lesions. Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imagining (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

b. Nonmeasurable Tumor Lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

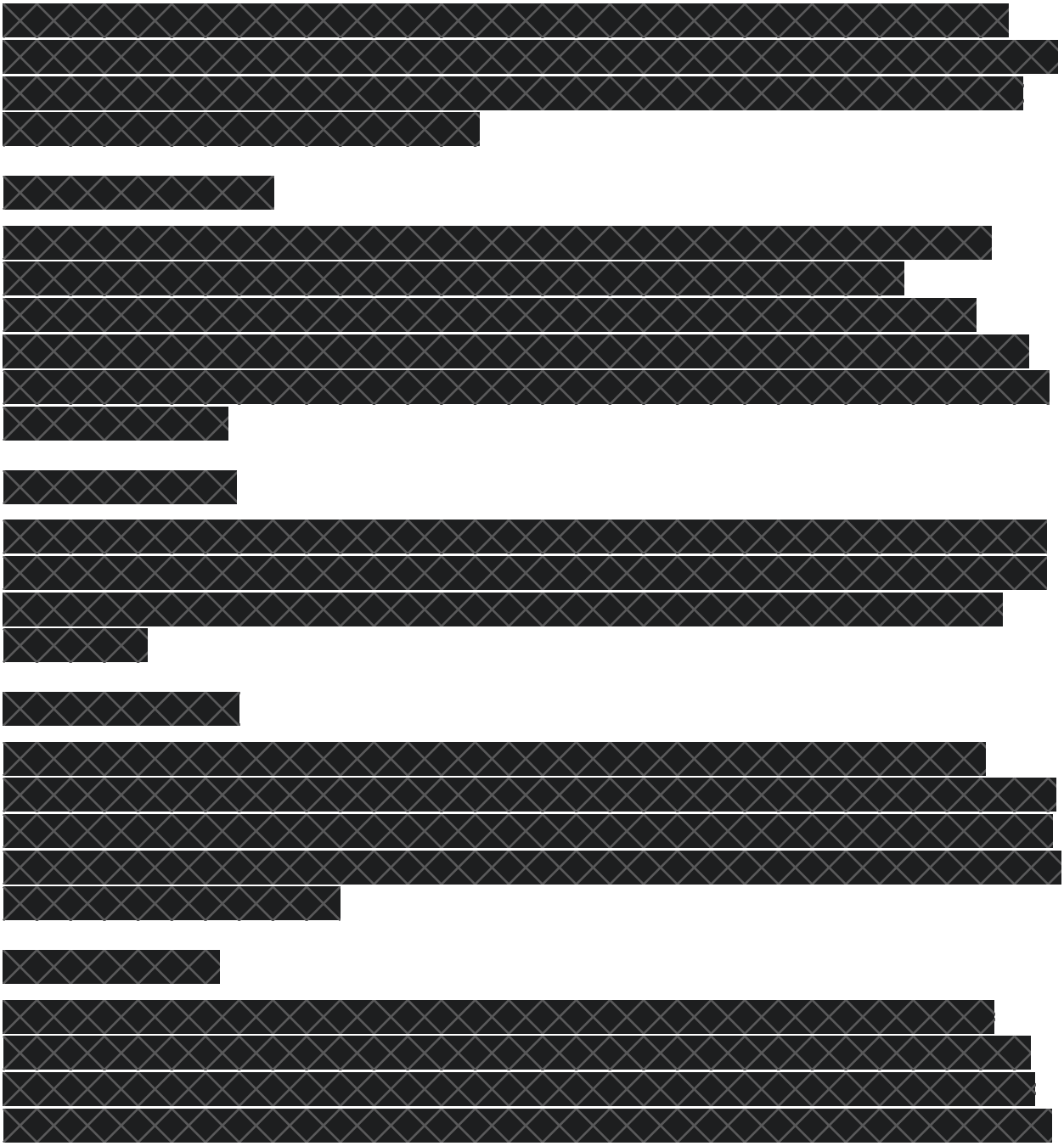
- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

MEASUREMENT OF LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

METHODS OF ASSESSMENT



TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF "TARGET" AND "NONTARGET" LESIONS

[redacted]

[redacted]

Lymph Nodes

[redacted]

Sum of Diameters

[redacted]

[redacted]

[redacted]

[redacted]

RESPONSE CRITERIA

a. Evaluation of Target Lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm).
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. NOTE: the appearance of one or more new lesions is also considered progression.

b. Special Notes on Assessment of Target Lesions

Lymph Nodes:

[redacted]

Target Lesions that Become "Too Small to Measure":

[redacted]

[redacted]

[redacted]

Lesions that Split or Coalesce on Treatment:

[redacted]

c. Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

Response	Evaluation of Nontarget Lesions
Complete Response (CR)	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis)
Non-CR/ Non-PD	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal existing non-target

[redacted]

d. Special Notes on Assessment of Progression of Non-target Disease

When the Patient also has Measurable Disease

[redacted]

When the Patient Has Only Nonmeasurable Disease

[redacted]

e. New Lesions

[redacted]

[redacted]

[redacted]

[redacted]

f. FDG-PET

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table A6-1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have nonmeasurable (therefore non-target) disease only, Table A6-2 is to be used.

Table A6-1 Timepoint Response: Patients with Target Lesions (with or without Non-target Lesions)

Target Lesions	Nontarget Lesions	New Lesion?	Overall Response
CR	CR	No	CR
CR	NonCR/NonPD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Table A6-2 Timepoint Response: Patients with Non-target Lesions Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Unevaluable Designation

[redacted]

c. Best Overall Response: All Timepoints

[redacted]

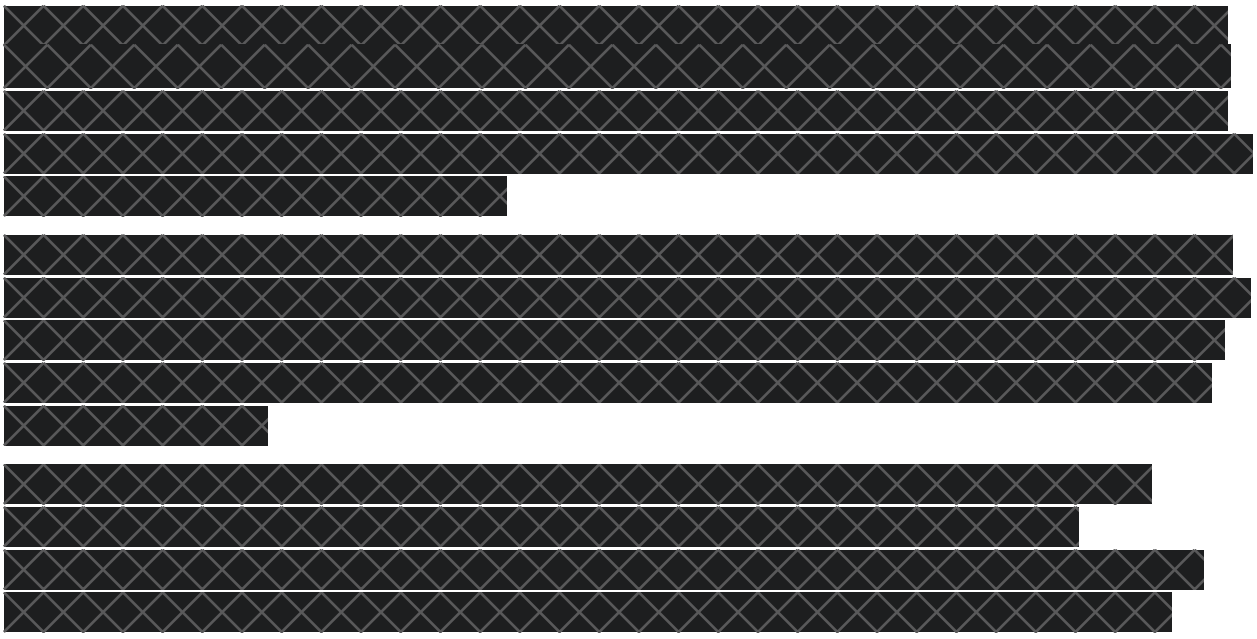
Table A6-3 Best Overall Response when Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] If a CR is truly met at the first timepoint, any disease n at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes on Response Assessment



[redacted]

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

APPENDIX 8 MEDICATION CLASSES THAT POTENTIALLY PROLONG QTC AND STRONG CYP3A INHIBITORS AND/OR INDUCERS

A partial list of drug classes that potentially prolong QTc and drugs that are strong CYP3A inhibitors and/or inducers is provided below.

Medications known to prolong QTc		
Amiodarone	Anagrelide	Arsenic Trioxide
Azithromycin	Chloroquine	Chlorpromazine
Cilostazol	Ciprofloxacin	Citalopram
Disopyramide	Dofetilide	Donepezil
Dronedarone	Droperidol	Erythromycin
Escitalopram	Flecainide	Fluconazole
Haloperidol	Ibutilide	Levofloxacin
Methadone	Moxifloxacin	Ondansetron
Oxaliplatin	Pentamidine	Pimozide
Procainamide	Propofol	Quinidine
Sevoflurane	Sotalol	Thioridazine
Vandetanib		
Strong CYP3A Inhibitors		
Boceprevir	Itraconazole	Ritonavir
Clarithromycin	Ketoconazole	Saquinavir and ritonavir
Cobicistat	Lopinavir and ritonavir	Telaprevir
Danoprevir and ritonavir	Nefazodone	Tipranavir and ritonavir
Elvitegravir and ritonavir	Nelfinavir	Telithromycin
Grapefruit juice	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	Troleandomycin
Idelalisib	Posaconazole	Voriconazole
Indinavir and ritonavir		
Moderate CYP3A Inhibitors		
Aprepitant	Diltiazam	Imatinib
Ciprofloxacin	Dronedarone	Tofisopam
Conivaptan	Erythromycin	Verapamil
Crizotinib	Fluconazole	
Cyclosporine	Fluvoxamine	

Strong CYP3A Inducers		
Apalutamide	Mitotane	St. John's wort
Carbamazepine	Phenytoin	
Enzalutamide	Rifampin	
Moderate CYP3A Inducers		
Bosentan	Phenobarbital	
Efavirenz	Primidone	
Etravirine		
Proton Pump Inhibitors (PPIs) – Excluded only during the dose escalation portion of the study		
Omeprazole	Lansoprazole	Dexlansoprazole
Rabeprazole	Pantoprazole	Esomeprazole
H-2 Receptor Antagonists – Excluded only during the dose escalation portion of the study		
Ranitidine	Famotidine	Cimetidine
Nizatidine		
Strong P-gp Inhibitors		
Amiodarone	Carvedilol	Clarithromycin
Dronedarone	Itraconazole	Lapatinib
Lopinavir and Ritonavir	Propafenone	Quinidine
Ranolazine	Ritonavir	Saquinavir and Ritonavir
Telaprevir	Tipranavir and Ritonavir	Verapamil

Please note that this list is not comprehensive.

The list and updates of medications that are known to prolong QTc may be obtained from www.crediblemeds.org.

For additional information and updates concerning strong CYP3A inhibitors and inducers and strong P-gp inhibitors, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition, consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. Contact the Medical Monitor if questions arise regarding medications not listed.

APPENDIX 9 GENOTYPIC MUTATIONS REQUIRED FOR ENROLLMENT

9A GENOTYPIC MUTATIONS REQUIRED FOR ENROLLMENT OF RMC-4630 AND COBIMETINIB STUDY

9B GENOTYPIC MUTATIONS REQUIRED FOR ENROLLMENT OF RMC-4630 AND OSIMERTINIB STUDY DURING DOSE EXPANSION

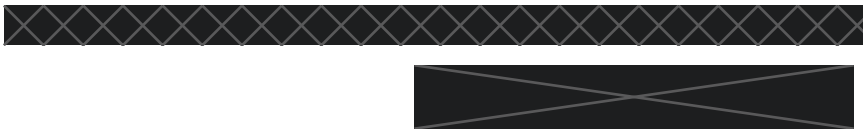
[redacted]

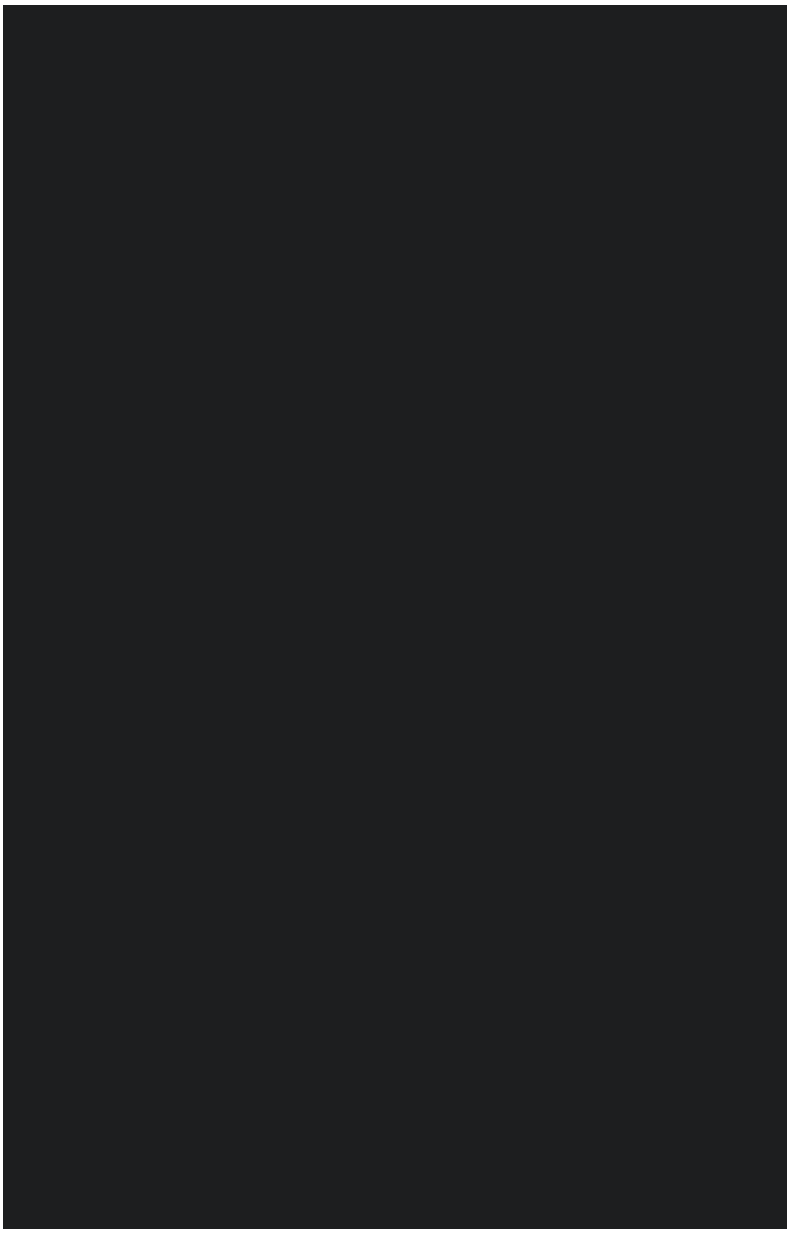
APPENDIX 10 [redacted]

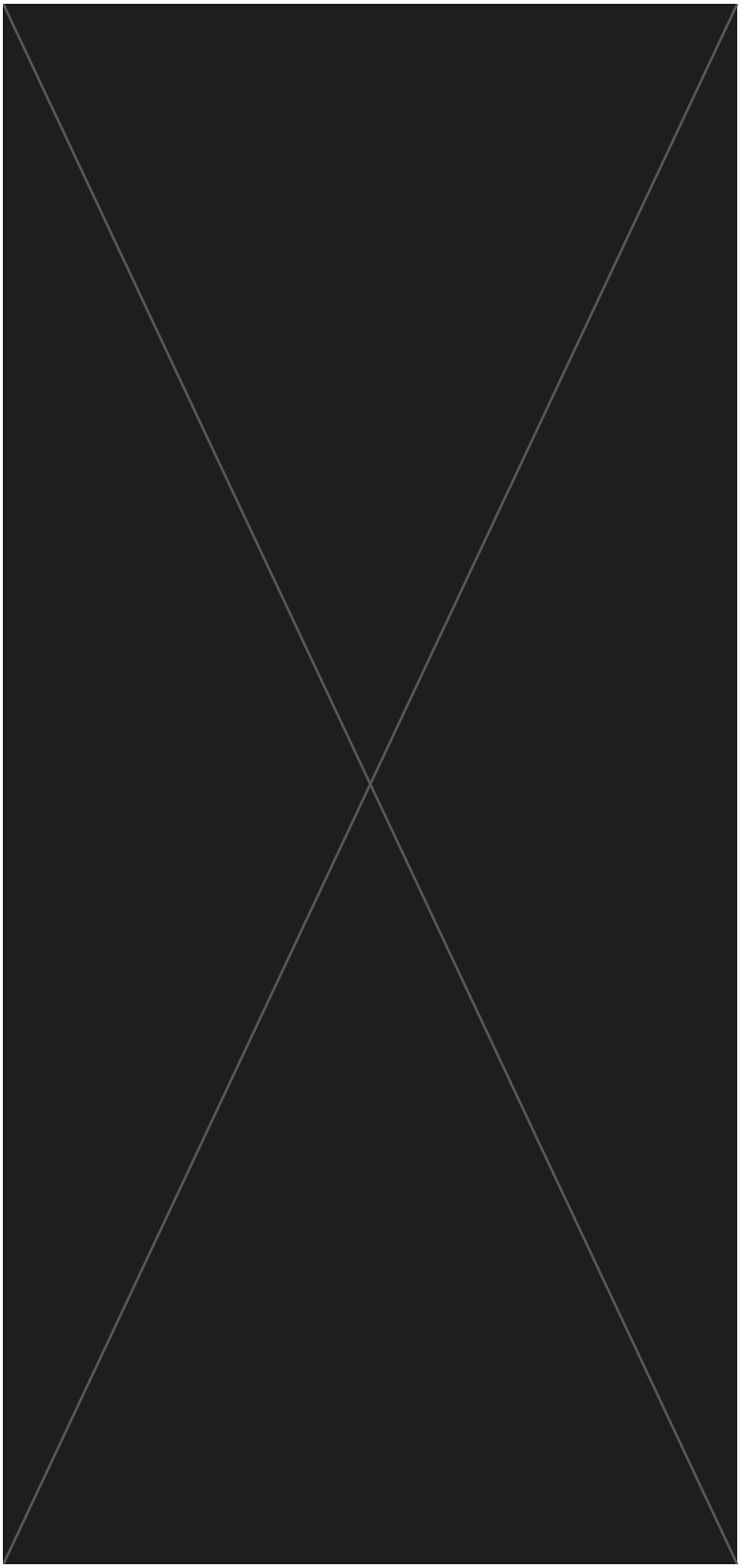
[redacted]

[redacted]

[redacted]







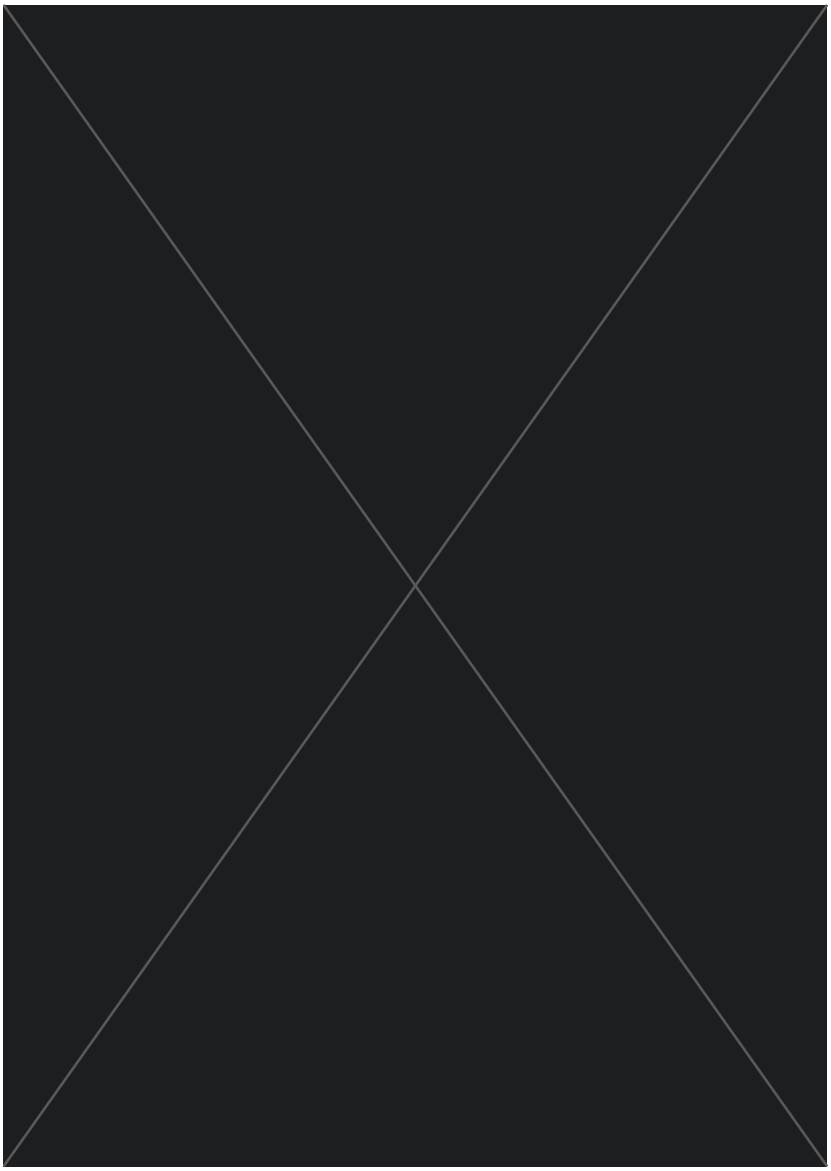
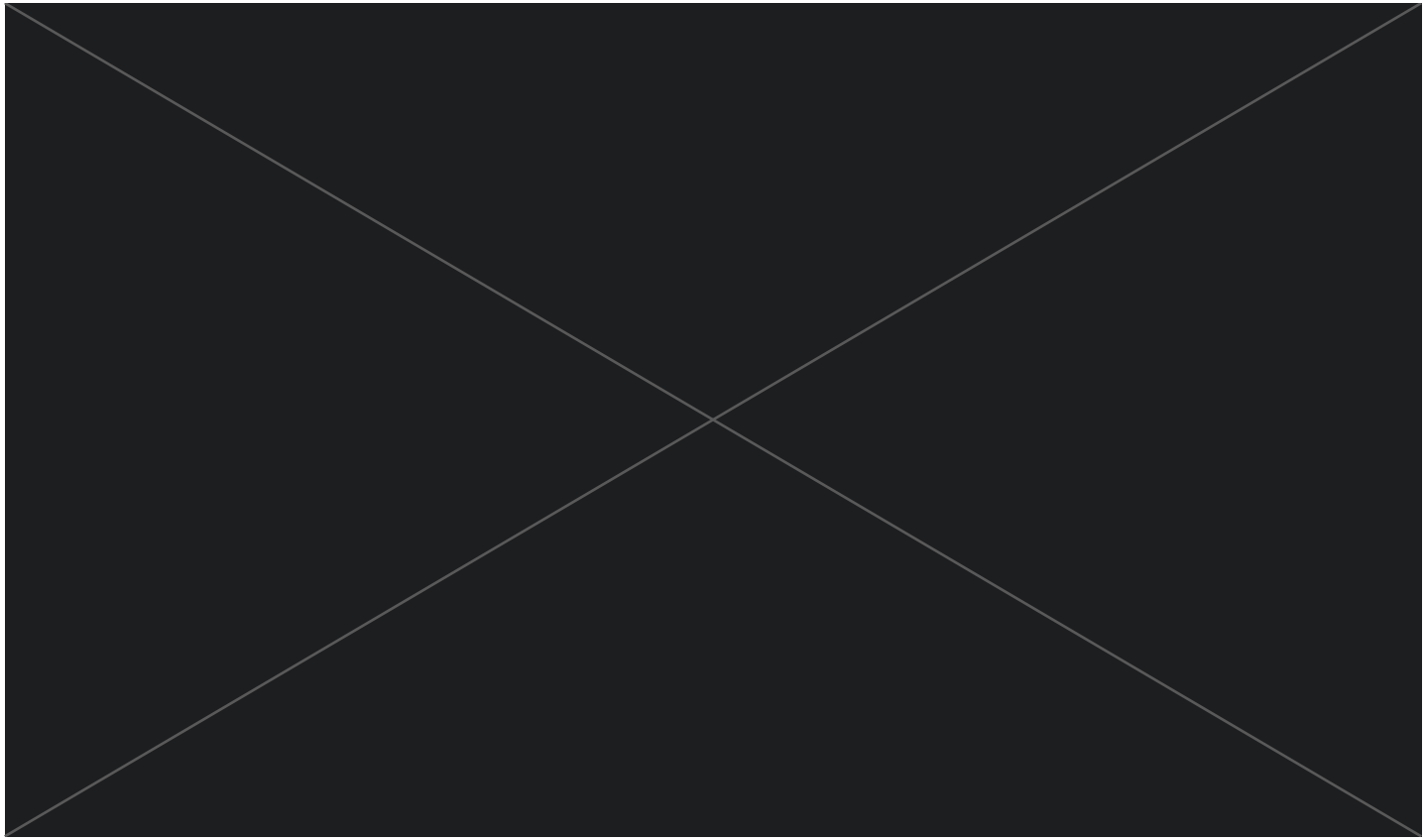
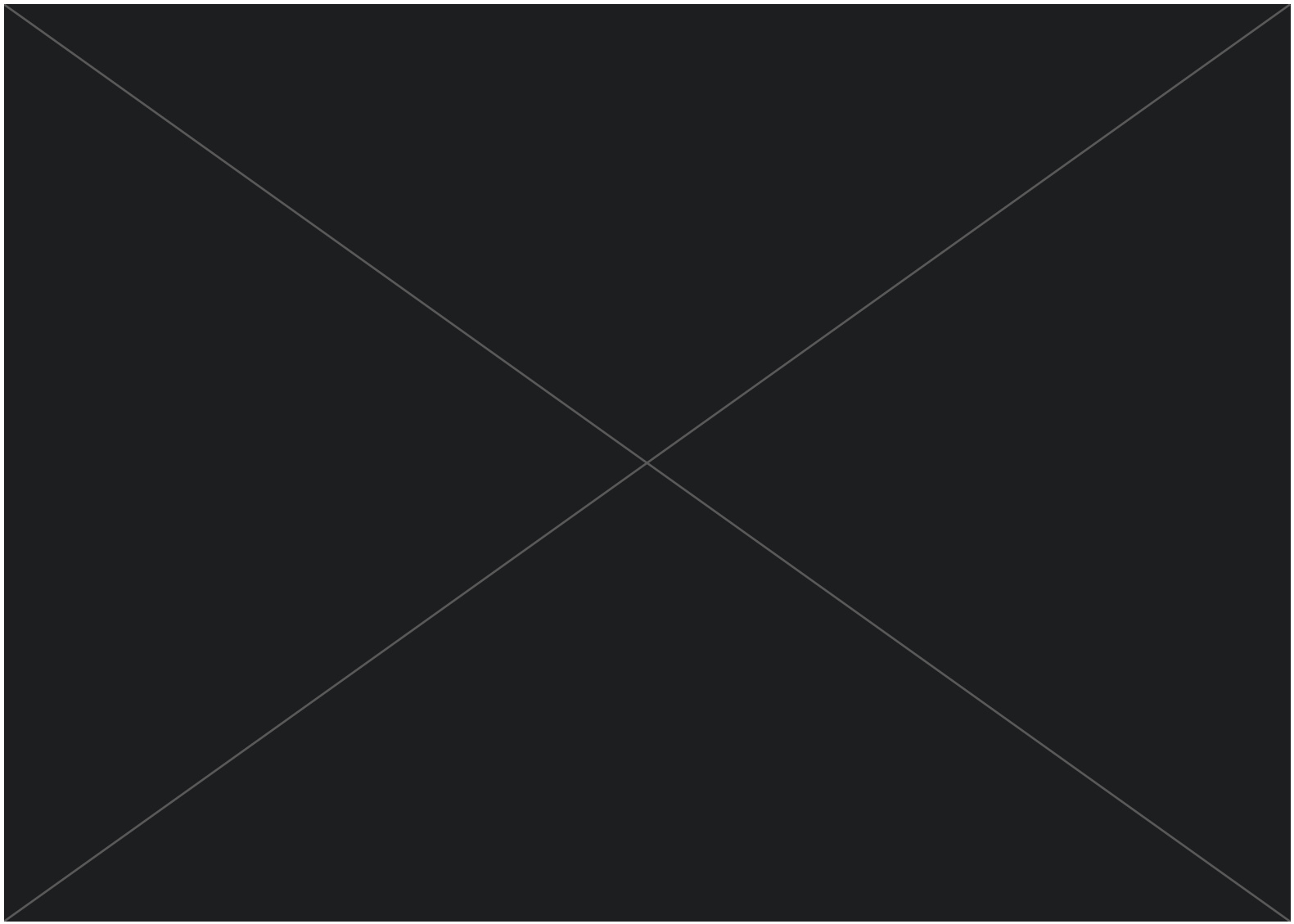
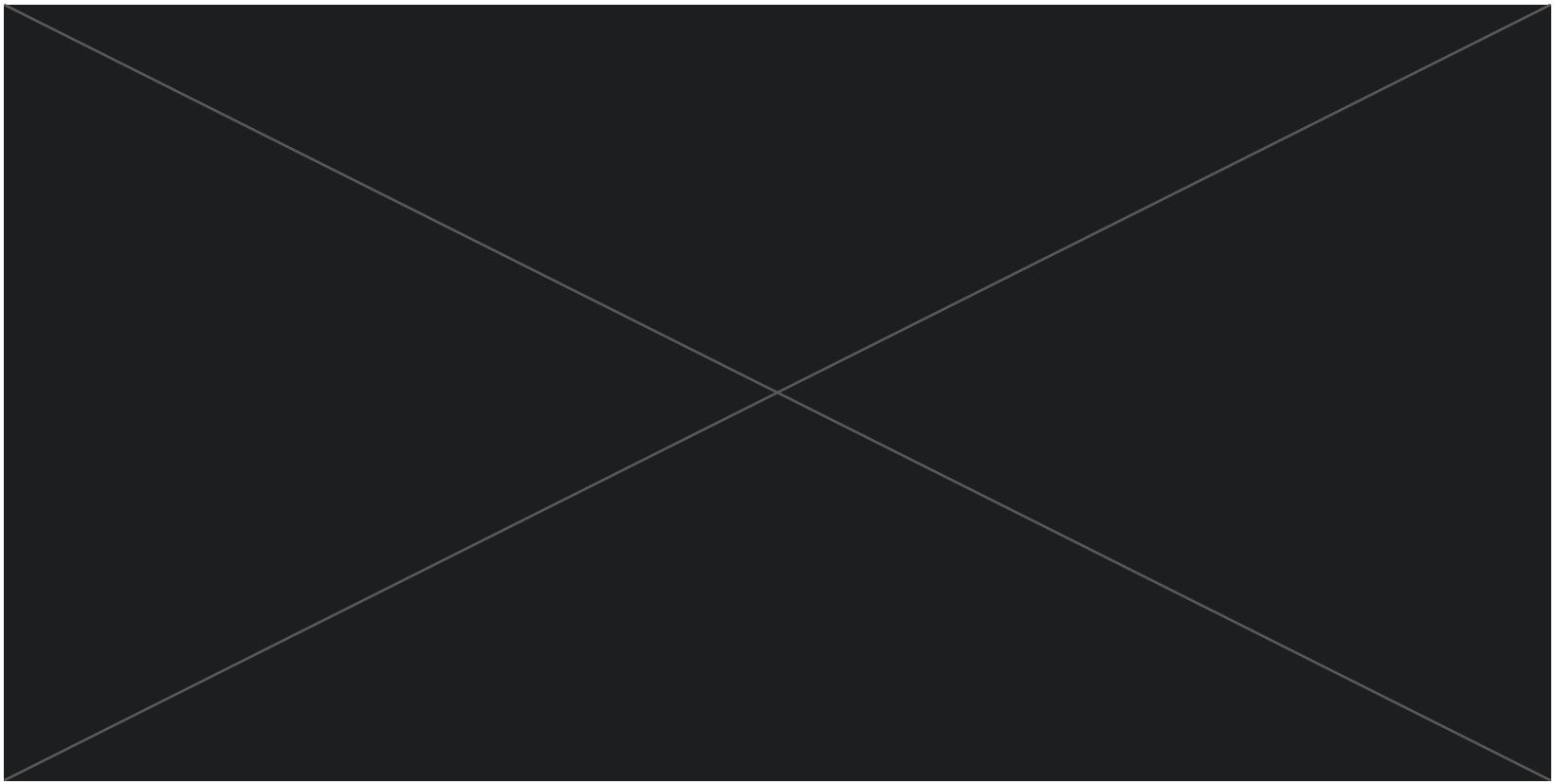


Table A10-2 [redacted]



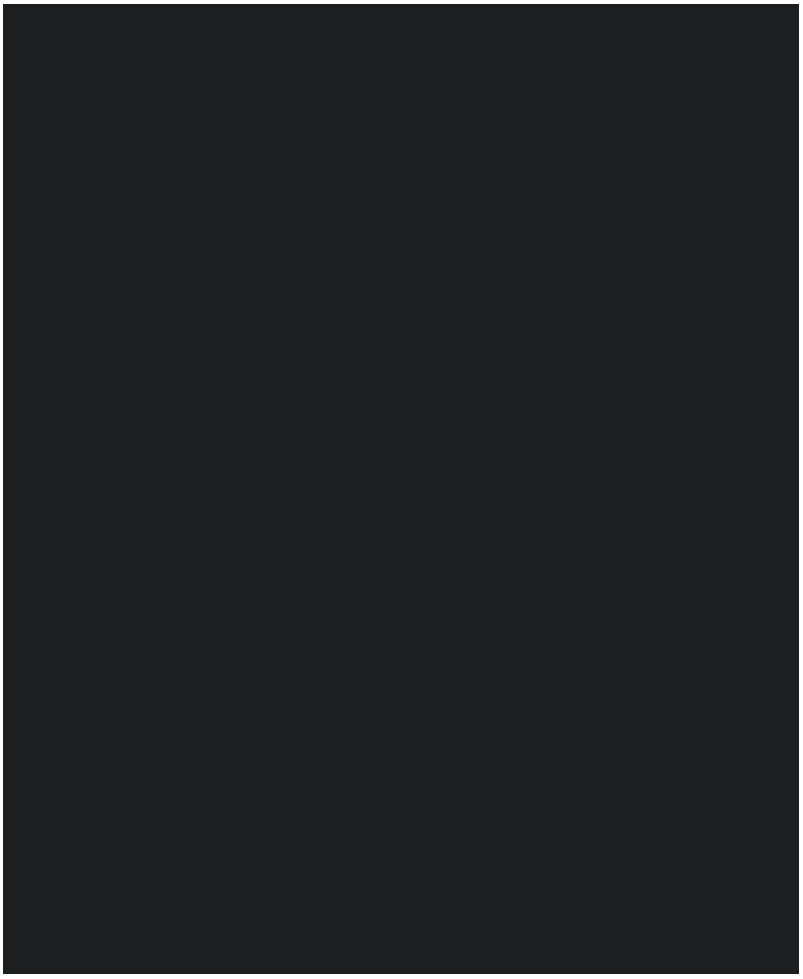


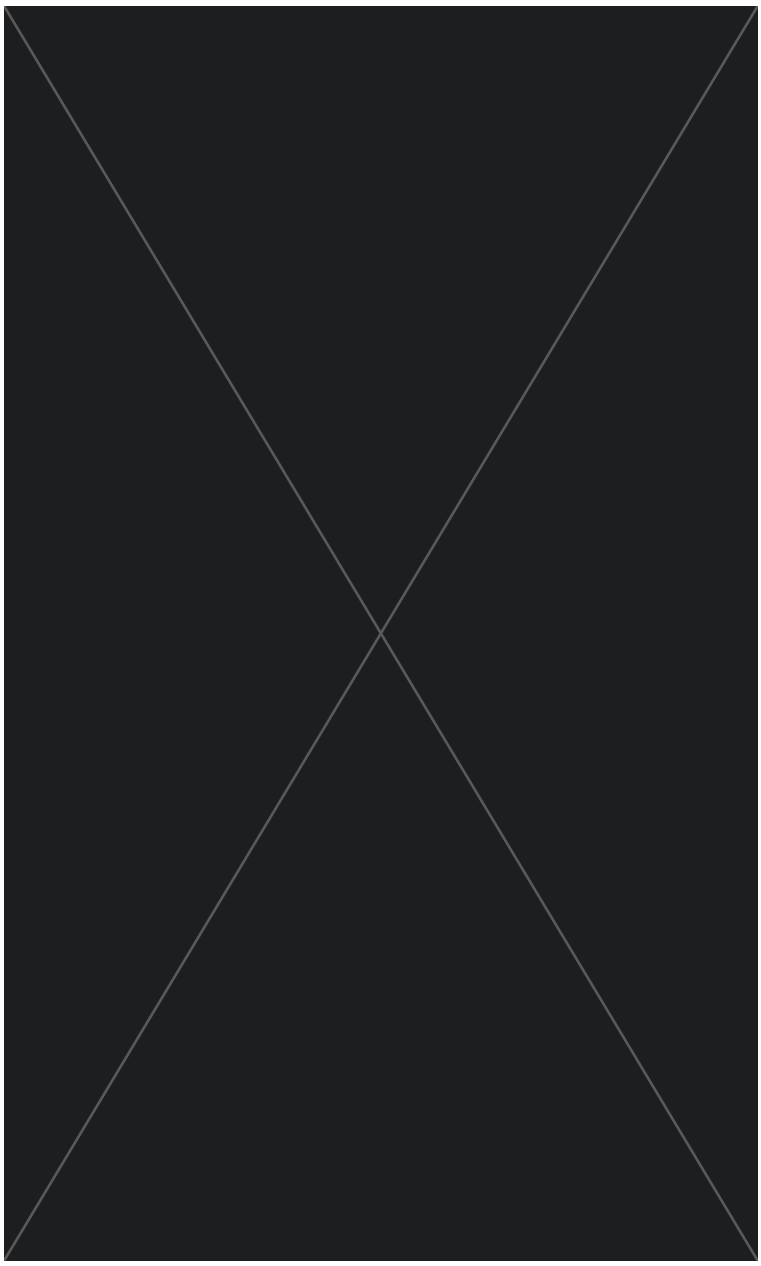


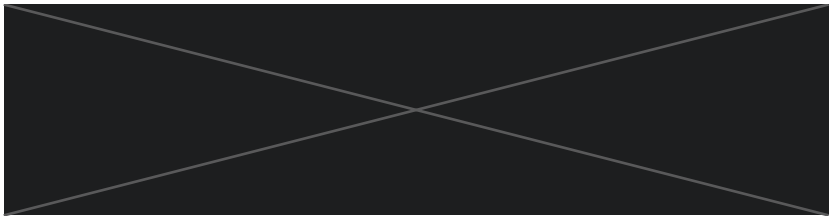
Conclusions

[redacted]

Table A10-3 Case Studies for RMC-4630 and Cobimetinib







APPENDIX 11 ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the curve from dosing time to time t
AUC_{inf}	area under the curve from dosing time to infinity
BCVA	best corrected visual acuity
BIW	twice weekly
[redacted]	[redacted]
BRAT	banana, rice, apples, toast
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
C_{max}	peak concentration
CNS	central nervous system
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRM	continual reassessment method
CRO	contract research organization
CSR	central serous retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

Abbreviation	Definition
EGFR	epidermal growth factor receptor
EMM	erythema multiforme major
EOT	End of Treatment
FFPE	formalin fixed, paraffin embedded
FDA	Food and Drug Administration
GAP	GTPase activating protein
GCP	Good Clinical practice
GDP	guanosine diphosphate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GTP	guanosine triphosphate
HCV	hepatitis C virus
HDPE	high-density polyethylene
HEENT	head, eyes, ears, nose, and throat
hERG	human Ether-à go-go
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
ISMC	Internal Safety Monitoring Committee
LLN	lower limit of normal
LMWH	low molecular weight heparin
LPLV	last participant, last visit
LVEF	left ventricular ejection fraction
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MCMC	Markov Chain Monte Carlo
MRI	magnetic resonance imaging

Abbreviation	Definition
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NE	not evaluable
[redacted]	[redacted]
[redacted]	[redacted]
NIH	National Institute of Health
NSCLC	non–small-cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
pERK	phosphorylated extracellular signal regulated kinase
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	oral(ly)
PR	partial response
PT	prothrombin time
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RTK	receptor tyrosine kinase
RVO	retinal vein occlusion
SAE	serious adverse event
SD	stable disease
SHP2	Src Homology 2 domain-containing protein tyrosine phosphatase 2
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
$t_{1/2}$	elimination half-life

Abbreviation	Definition
T_{max}	time to achieve peak concentration
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential