Cover page

Document title: A Multi-arm, Phase II, Open-Label, Multicentre Study to Assess the Preliminary Efficacy of RXC004 in Monotherapy and in Combination with Nivolumab, in Patients with Ring Finger Protein 43 (RNF43) or R-spondin (RSPO) Aberrated, Metastatic, Microsatellite Stable, Colorectal Cancer who have Progressed following Therapy with Current Standard of Care

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Clinical Study Protocol RXC004/0002

A Multi-arm, Phase II, Open-Label, Multicentre Study to Assess the Preliminary Efficacy of RXC004 in Monotherapy and in Combination with Nivolumab, in Patients with Ring Finger Protein 43 (RNF43) or R-spondin (RSPO) Aberrated, Metastatic, Microsatellite Stable, Colorectal Cancer who have Progressed following Therapy with Current Standard of Care

Statistical Analysis Plan

Version: 4.0

Parexel Project Number: 253582

SPONSOR SIGNATURE PAGE

This document has been approved and signed electronically by the following:

	Signatory
Reviewer	PPD Project Role: PPD
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Parexel SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically by the following:

	Signatory
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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	25-Mar-2021	New document
2.0	25-Jan-2022	SMC meeting Revision of Adverse Events section (Outputs added, AEPI, Dysgeusia assessment) Add Bones evaluation Add eDISH plots Add Dysgeusia evaluation
3.0	21-Sep-2023	Revision of Evaluable Set definition Add new variables in Baseline Characteristics Revision of RDI definitions Revision of sorting rules for AEs and ConMeds Add CCI analysis
4.0	24-May-2024	Revision Objectives endpoints definition Revision Evaluable Set definition Revision Concomitant Medications imputation rules Add CCI imputation rules Add Labs BLQ rules

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC from time zero extrapolated to infinity
BMI	Body Mass Index
BOR	Best Overall Response
C0	Cycle 0
CI	Confidence Interval
CL/F	Apparent clearance following oral administration
eCRF	electronic Case Report Form
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration in the dosing interval
CR	Complete Response
CRC	Colorectal Cancer
CT	Computerized Tomography
DCO	Data Cut-Off
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
EoS	End of Study
FAS	Full Analysis Set

Abbreviation / Acronym	Definition / Expansion
Hb	Hemoglobin
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
LRV	Lower Reference Value
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSS	Microsatellite stable
NE	Not evaluable
NLs	New Lesions
NTL	Non-Target Lesions
OR	Overall Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease only use one abbrev, do not use pharmacodynamics or protocol deviation, spell those out
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNF43	Right Finger Protein 43
RP2D	Recommended Phase 2 Dose
RSPO	R-spondin

Abbreviation / Acronym	Definition / Expansion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease, do not use standard deviation or single dose, spell those out, they are not frequently mentioned in this document
SI	System of Units
SoA	Schedule of Assessments
SOC	System Organ Class
SLD	Sum of Longest Diameters
TEAE	Treatment-emergent adverse event
TFLs	Tables/Figures/Listings
TLs	Target Lesions
t_{max}	Time corresponding to occurrence of C_{max}
TSH	Thyroid Stimulating Hormone
TTR	Time To Response
TV	Target Value
UK, UKN, UNKN	Unknown
VS	Vital signs
V_z/F	Apparent volume of distribution during terminal phase
WHO-DD	World Health Organization - Drug Dictionary
Wnt	Wingless Int-1 (pathway)
λ_z	Terminal elimination rate constant

1 INTRODUCTION

The analyses described in this statistical analysis plan (SAP) are based upon the following study documents:

- Study Protocol, Version 7.0 (19-Aug-2022)
- electronic Case Report Form (eCRF), Version 3.0 (09-Jun-2022)

The structure and content are based upon International Conference on Harmonization (ICH) requirements as detailed in ICH E3 – Structure and Content of Clinical Study Reports [8].

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2 STUDY OBJECTIVES

Objectives	Endpoints
Primary	
To assess the anti-tumour activity of RXC004 monotherapy and RXC004 + Nivolumab	Monotherapy: Disease control rate (DCR) using each patients Best Overall Response (BOR) according to RECIST 1.1 Combination: Objective response rate (ORR) using each patients BOR according to RECIST 1.1
Secondary	
To further assess the preliminary efficacy of RXC004 monotherapy and RXC004 + Nivolumab	% change in the sum of target lesions, duration of response (DoR), PFS, ORR (monotherapy) and DCR (combination) using investigator assessments according to RECIST 1.1 and OS
To assess the PK of RXC004 in monotherapy and in combination with Nivolumab	Maximum plasma concentration (Cmax) after Dose 1, Cmax at steady state, minimum observed plasma concentration (Cmin) at steady state as well as other relevant parameters (e.g. tmax, t½, λz, AUC0-∞, CL/F, and Vz/F)
To assess the safety and tolerability profile of RXC004 monotherapy and RXC004 + Nivolumab combination	Incidence of AEs SAEs, dose reductions, interruptions and discontinuation and assessment of dysgeusia
Exploratory	
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3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase II, open label, multicentre, multi-arm, study to evaluate the preliminary efficacy and safety of RXC004 as monotherapy and in combination with Nivolumab in patients with Ring finger protein 43 (RNF43) or R-spondin (RSPO) aberrated, microsatellite stable (MSS) colorectal cancer (CRC), who have progressed following current standard of care treatment.

The study is composed of two arms:

- RXC004 monotherapy (arm A).
- RXC004 in combination with Nivolumab (arm B).

20 eligible patients will be enrolled in arm A and 20 eligible patients in arm B.

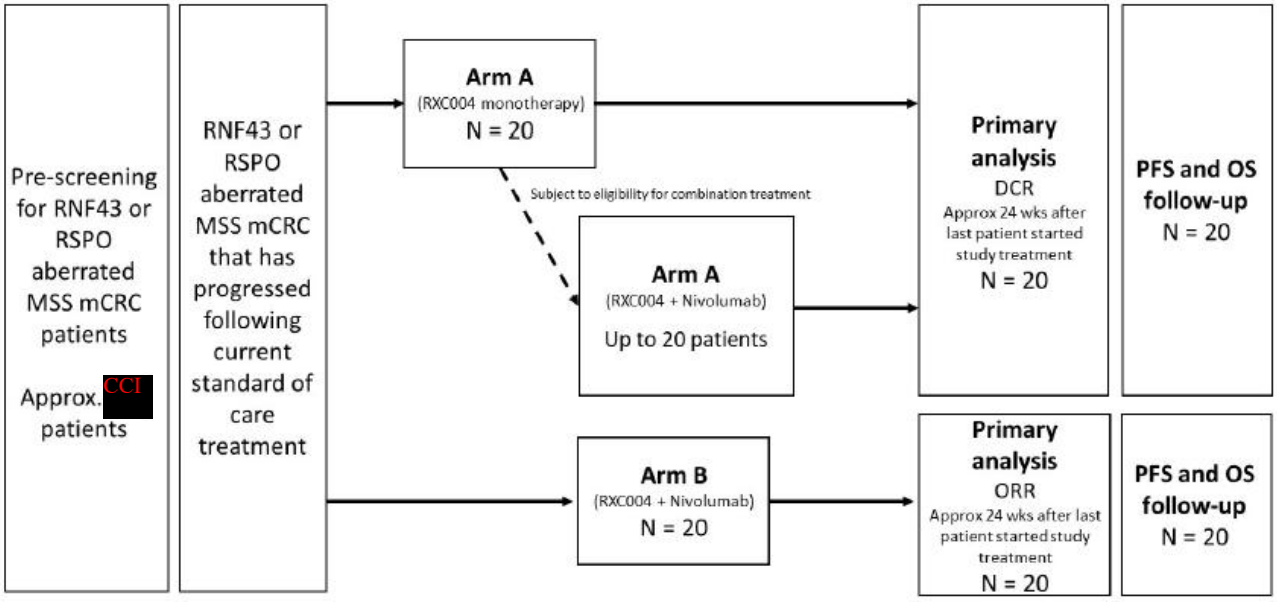
The study will initially open with arm A. arm B will be opened once a recommended Phase II dose (RP2D) for RXC004 in combination with Nivolumab is established in the Phase I dose escalation study (NCI 03447470).

Patients in arm A may be treated with RXC004 + Nivolumab if they have progressive disease on the 8-week scan (a protocol amendment with RP2D details of RXC004 + Nivolumab will be required before the arm A combination treatment phase can be opened).

The primary objective of the study is to assess the preliminary efficacy of each treatment arm, RXC004 monotherapy (arm A) and RXC004 + Nivolumab (arm B), based on an individual patient's best overall response (BOR). Tumour assessment will be performed by Investigators every 8 weeks (± 1 week) (relative to the date of initiation of study treatment) for the first 56 weeks, and then every 12 weeks (± 1 week) until radiological progressive disease (PD) (as defined by Response Evaluation Criteria in Solid Tumours, version 1.1 [RECIST 1.1] [9]). The primary efficacy endpoint for RXC004 monotherapy is the disease control rate (DCR) (i.e. the proportion of patients who achieve complete response [CR], partial response [PR] or stable disease [SD]), and the primary efficacy endpoint for RXC004 + Nivolumab is the objective response rate (ORR) (i.e. the proportion

of patients who achieve CR or PR). Following radiological progression, patients will be followed-up for safety and survival. The general study design is summarized in Figure 1.

Figure 1 - Overall Design



DCR disease control rate, ECOG performance status, LoF, mCRC metastatic colorectal cancer; MSS Microsatellite stable; ORR objective response rate; OS Overall survival; PFS progression free survival; RNF43 Ring finger 43; RSPO R-Spondin; RXC004 Porcupine inhibitor

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Variables

The following variables will be used to evaluate efficacy endpoints:

- In accordance with RECIST 1.1 guidelines (see Section 6.1):
  - ORR based on each patient's BOR
  - DCR based on each patient's BOR
  - Percentage change at each visit and best overall percentage change in the sum of target lesions
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Time to Response (TTR)
- Overall Survival (OS)

In case the RECIST 1.1 assessment is done across several days:

- The first day of assessment will be considered in case of PD as Overall Response (OR).
- The last day of assessment will be considered in case of response (CR, PR or SD) as OR.

3.2.1.1 Best Overall Response (BOR)

BOR is defined as the best OR recorded from the start of the study treatment until PD or death for each patient. In case the progression event is death, the BOR takes into account all data collected until the last evaluable RECIST assessment before death. Only OR provided by Investigators at each RECIST 1.1 visit will be considered for variables derivation and analyses (for details, see Section 6.1).

Confirmation of response is required for declaring PR or CR as BOR. BOR is determined once all data on OR for the patient are known. BOR will be computed as the key efficacy variable to determine ORR and DCR.

A confirmed response is defined as a CR or PR followed by a CR or PR a least 4 weeks later (see Table 1 – Determination of Best Overall Response). A requirement for SD is that it should be met at least once no less than 8 weeks after the first dose of trial treatment/baseline assessment, otherwise the best response will be considered as not evaluable (NE) according to RECIST 1.1 guidelines. As the protocol allows a window of 1 week for the scan, a scan at least 7 weeks from start of treatment will be acceptable for SD.

Table 1 – Determination of Best Overall Response (RECIST 1.1 BOR determination in trials where confirmation of complete or partial response is required)

Overall response first time point	Overall response subsequent time point (at least 4-weeks after)	Best Overall Response
CR	CR	CR
CR	PR	see footnote (*)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

(*) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether 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 time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

3.2.1.2 Objective Response Rate (ORR)

ORR is defined as the proportion of patients with a BOR of CR or PR. Confirmation of response is required for declaring PR or CR as the BOR. ORR was set as primary efficacy endpoint for arm B and secondary efficacy endpoint for arm A. Responses on subsequent treatments after discontinuing will not be included.

3.2.1.3 Disease Control Rate (DCR)

DCR is defined as the proportion of patients with a BOR of either CR, PR or SD for at least 16 weeks post-baseline (corresponding to SD for 2 scheduled scans post-baseline). As the protocol allows a window of 1 week for the scan, a time window of 1 week before the Week 16 visit will be applied such that any scan that is at least 15 weeks after starting treatment will be considered acceptable for the evaluation of response. DCR was set as primary efficacy endpoint for arm A and secondary efficacy endpoint for arm B. As an additional analysis, DCR will also be defined as the proportion of patients with a BOR of either CR, PR or SD for at least 8 weeks post-baseline (corresponding to SD for 1 scheduled scan post-baseline). As the protocol allows a window of 1 week for the scan, a time window of 1 week before the Week 8 visit will be applied such that any scan that is at least 7 weeks after starting treatment will be considered acceptable for the evaluation of response.

3.2.1.4 Percentage change in the sum of target lesions

Percentage change in sum of diameters of target lesions from baseline for patients with measurable disease, will be calculated for each RECIST assessment visit, as follows:

Percentage change in the sum of target lesions (%) = (Σ observed value after baseline - Σ observed value at baseline) * 100 / Σ observed value at baseline

Percentage change in sum of diameters of target lesions was set as a secondary efficacy endpoint for both arm A and arm B.

The best overall percentage change in the sum of target lesions (%), representing the largest decrease (or smallest increase in the absence of a decrease) from baseline, will also be considered as an efficacy endpoint.

3.2.1.5 Progression Free Survival (PFS)

PFS is defined as the time from first dose of study treatment (Day 1) until the date of disease progression or death (by any cause in the absence of progression), regardless whether the patient withdraws from the assigned study treatment or receives another anticancer prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of RECIST 1.1 assessment of their last evaluable scan, however if the patient progresses or dies after 2 or more missed scheduled scanning visits (Progression/Death date - Last available scan date>=16 +1 weeks), the patient will be censored at the time of their last evaluable scan prior to the missing scan visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days. However, if the patient dies within 2 scan visits of first dose (within 16 +1 weeks from first dose date without a post baseline scan) then its death date will be treated as their progression date. PFS was set as secondary efficacy endpoint both for arm A and arm B, and PFS time is defined as:

PFS (days) = Date of documented PD, Death or last RECIST 1.1 assessment – first dose of study treatment (C0D1) + 1

3.2.1.6 Overall Survival (OS)

OS is defined as the time from the first day of study treatment (Day 1) until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. OS was set as secondary efficacy endpoint both for arm A and arm B, and OS time is defined as:

OS (days) = Date of death or last contact – first dose of study treatment (C0D1) + 1

3.2.2 Pharmacokinetic/Pharmacodynamic Variables

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3.2.3 Safety Variables

The following safety variables will be evaluated:

- AEs and SAEs
- Dysgeusia
- Vital signs

- Electrocardiogram (ECG)
- ECOG performance status
- Prior and concomitant medications
- Clinical laboratory evaluation
- Bones evaluation

3.2.4 Exploratory Variables

Methods for evaluation of CCI [redacted] will be provided in a separate SAP.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

Tables/Figures/Listings (TFLs) to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

All tables, listings, and graphs will be produced to landscape orientation using Courier New 9pt font and will be incorporated into a MS Word document as a rich text file (RTF) (margins on standard A4: Margins (top, left, right, and bottom) 2.54 cm.

4.2.1 Study Days

Screening will be conducted between Day -28 and Day -1. The first day of treatment will be Cycle 0 - Day 1 (C0D1). When calculating AEs/ConMeds/etc timing days will be calculated relative to day 1.

For patients in arm A, who have radiologically progressed at Week 8 and move to RXC004 + Nivolumab, count of days will re-start from the day of the first of intake of the combination a new Cycle 1 with D1, as reported in the Schedule of Activities (SoA) (see protocol).

4.2.2 Visit Windowing

By visit summaries will be made considering the windows as below. The visit windowing is assessed relative to C1D1 date (not C0D1 due to delays between C0D1 and C1D1).

C0D1	C0D1
C1D1	(C1D1 - Day 8)
Day 15	(Day 9 - Day 21)
Day 29	(Day 22 - Day 42)
Day 57	(Day 43 - Day 70)

Day 85	(Day 71 - Day 98)
Day 113	(Day 99 - Day 126)
Day 141	(Day 127 - Day 154)
Day 169	(Day 155 - Day 182)
Day 197	(Day 183 - Day 210)
Day 225	(Day 211 - Day 238)
Day 253	(Day 239 - Day 266)
Day 281	(Day 267 - Day 294)
Day 309	(Day 295 - Day 322)
Day 337	(Day 323 - Day 350)
Day 365	(Day 351 - Day 378)
Day 393	(Day 379 - Day 406)
Day 421	(Day 407 - Day 434)
Day 449	(Day 435 - Day 462)
Day 477	(Day 463 - Day 490)

The following visits will not be remapped: Screening, IP Discontinuation, 30/90 Day Follow-up, Survival Follow-up.

In case several visits occur into the same windows the following rule is to be applied:

- For by-visit table, we will consider the mean of available assessments.
- For Shift table, we will consider either Minimum or Maximum available value depending on the direction.

4.2.3 Definition of Baseline and Post-baseline Assessments

A baseline assessment will be defined as the last assessment performed prior to the first dose of study treatment (C0D1). While many of these assessments will be performed on the day of the first dose, others will be performed during screening. If a patient is missing an assessment typically performed on the day of the first dose, screening values may be substituted as baseline.

Patients treated with RXC004 monotherapy (arm A) that radiologically progress as per RECIST1.1 at the first 'on treatment' scan, may be treated with RXC004 + Nivolumab combination. Accordingly, the following groups of analyses have to be defined to clarify which patients and which information in arm A will be utilized:

- **Arm A (RXC004 monotherapy):** this group will include information for all patients enrolled in arm A.
- **Arm A1 (RXC004 monotherapy):** this group will include information of all patients enrolled in Arm A who were on monotherapy throughout the study - ie. subjects who did not radiologically progressed at the first scan (week 8) or who radiologically progressed

at the first scan (week 8) but remained on monotherapy or who withdrew before the first scan.

- **Arm A2 (RXC004 + Nivolumab):** this group will include information of patients enrolled in arm A who radiologically progressed at the first scan (Week 8) and then switch to receive combination therapy of RXC004 + Nivolumab either at Week 8 or later. The last scan before the switch to combination treatment will be set as the arm A2 baseline RECIST1.1 scan for the combination treatment. The date of the last scan before switching to combination treatment will also be used to determine the arm A2 baseline date for all the efficacy endpoints except OS. OS will keep the same baseline regardless of the progression. For assessments other than efficacy, Arm A2 summaries, will include data from start of monotherapy until end of combination treatment.
- **Arm B (RXC004 + Nivolumab):** this group will include information on all patients enrolled in arm B.

Some patients with symptomatically stable disease may continue treatment after the initial RECIST 1.1 - defined progression, until symptomatic/clinical progression or a second RECIST 1.1 PD assessment (relative to the initial RECIST1.1 progression, for a given study treatment).

Change from baseline is derived where both baseline and post-baseline values are available:

- Absolute Change from baseline = post-baseline value – baseline value
- Relative Change from baseline (%) = [(post-baseline value – baseline value) / baseline value] * 100

4.2.4 End of Study (EoS)

A participant is considered to have completed the study if he/she has completed all phases of the study (including the last visit and the last scheduled assessment shown in the SoA) or withdraws consent whichever occurs first.

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled assessment shown in the SoA for the last participant in the study before the data cut off (DCO).

4.2.5 Data Listings

All listings will contain information both for arm A and arm B (arm A patients followed by arm B patients). Patients who change treatment in arm A after radiological progression at week 8 will be flagged.

All listings will include scheduled and unscheduled measurements. All listings will display the same number of decimals as in the source data. All raw data will be reported exactly as provided.

4.2.6 Data summaries

Summaries will be presented as follows:

- Arm A and arm B in the same table, as detailed described in the following sections. A separate set of tables and figures on selected endpoints will be done for arm A1 and/or arm A2.
- No formal comparisons will be performed between arms.

4.2.7 Figures

Figures for efficacy evaluation will be produced as detailed in Section 4.11. In selected presentations where specified, figures presenting arm A, arm A1, arm A2 and arm B will be produced. For arm A1 and arm A2, KM curves will be presented provided there enough data to make it meaningful to do so: at least 8 events.

4.2.8 Handling of Dropouts or Missing Data

There will be no imputation of missing data, unless otherwise stated.

4.2.9 Analysis Conventions

Continuous data will be summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations, unless otherwise stated.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median, will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Confidence intervals will be presented to one more decimal place than the raw data.

4.3 Software

TFLs and any non-descriptive statistical analysis will be produced using SAS® Software (Version 9.3 or higher). The REPORT procedure (SAS PROC REPORT) will be used to produce all table and listings; SAS/GRAPH will be used to produce all figures.

4.4 Study Patients

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided from screening to study completion.

The number of patients who were screened (who signed main study ICF), were exposed to study treatment, who completed the study or discontinued and primary reason for end of treatment will be summarized for arm A and arm B in the FAS. The number of patients in arm A who switch from monotherapy to combination therapy will also be summarized. The number of patients in arm A and arm B who remained on original treatment despite disease progression will also be presented.

The patient disposition including the date the informed consent was signed, date of first/last intake of study drug and the primary reason for End of Treatment will be listed.

A listing of patients included into each of the analysis set will be presented, related summary statistics will be provided. Patients who did not meet the eligibility criteria or were screen failures will also be listed.

4.4.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor in an ongoing manner during protocol deviation review meetings. Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. Protocol deviations are defined in the project-specific Protocol Deviation Specification. Whether a protocol deviation results in exclusion from a particular analysis set will be detailed in the protocol deviation specification and documented in the supporting protocol deviation review document.

The number and percentage of patients with major protocol deviations will be summarized by type of deviation for arm A and arm B in the FAS. The summary will be done separately for major protocol deviations leading to exclusion from the evaluable set and the other major protocol deviations. All protocol deviations will be listed.

4.5 Analysis Sets

A summary of the number of patients included in each analysis population described below will be provided for arm A and arm B. Percentage of subjects in the evaluable set will be calculated based on the full analysis set (FAS).

A listing of patients included into each of the analysis set will be presented will be provided. The patients who did not meet the eligibility criteria or were screen failures will also be listed.

- **Full analysis set (FAS) / Safety analysis set**: All patients who enrolled and received at least one dose of study drug (RXC004 in the case of the monotherapy arm and at least one of RXC004 or nivolumab in the combination arm).
- CCI [redacted]
- **PK analysis set**: All patients in the safety analysis set who have had at least 1 blood sample.

4.6 Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be summarized and listed for the FAS.

Demographics will be summarized for arm A and arm B, including:

- Age (years)
- Gender (Male or Female)
- Race (American Indian or Alaska Native, Asian, Black or African, American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Stated, Unknown)

Baseline characteristics will be summarized for arm A and arm B, including:

- Weight (kg)
- Height (only screening visit) (cm)
- Body Mass Index (BMI) result (kg/m2)
- ECOG PS at Study Entry
- Stage at Study Entry
- Primary Location
- Cancer Classification (Histology)
- Histological Grade
- TNM status
- MSI status
- WNT pathway genetic aberration (LoF RNF43 mutation, RSPO2/3 Fusion, Wild Type, No Results Available)
- PD-L1 Tumor proportion score: as continuous and categorical variable (<1%, >=1% - 49%, >50%)
- PD-L1 Immune proportion score: as continuous and categorical variable (<1%, >=1% - 49%, >50%)
- Site of Local/Metastatic Disease
- Number of prior lines of cancer therapy and indications
- Best response achieved for the most recent treatment
- Time from last Disease Progression disease to first dose of Study Drug (weeks)*
- Time from Initial Metastatic Diagnosis to first dose of Study Drug (Months)*
- Time from last most recent Dose of prior therapy to first dose of Study Drug (weeks)*
- Sum of target lesions at Baseline

(*) In case, last disease progression date, initial metastatic diagnosis date or most recent dose prior therapy date is incomplete, the following imputation rules will be implemented:

- UK-MMM-YYYY: Assume 01-MMM-YYYY.
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JUL-YYYY of the collected year. Otherwise, no imputation.
- UK-UKN- UNKN: No imputation. Duration will be considered as missing.

4.7 Medical History and Surgical History

Medical history and Surgical history as pre-specified in the Medical and Surgical history eCRF will be presented in the patient data listings.

4.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization - Drug Dictionary (WHO-DD) Version March 2023 and will be classified by Anatomical Therapeutic Chemical (ATC) categories. Prior medications will be defined as medications that stopped before the first dose of study drug and will be listed only.

For the purpose of categorizing medications as prior or concomitant, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug;
- UK-UKN-YYYY:
    - If the year is prior to the year of first dose of study drug, assume 01-JUL-YYYY of the collected year. If the end date is before 01-JUL-YYYY, assume the first day of the year.
    - If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug. If the End Date occurs before the first dose of study drug, then assume the first day of the year.
    - If the year is after the first dose of study drug year, then assume the first day of the year.
- UK-UKN- UNKN: Assume date of first dose of study drug. In case end date is before first dose of study drug, assume the first day of the year of the CM end date.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN- UNKN: Assume ongoing and leave it missing.

Medications will be categorized as follows:

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior or Concomitant.

Medications and treatments administered prior to the Investigational Medicinal Product (IMP) intake which stopped prior to IMP intake will be considered as prior medications. Medications and treatments which started before, on or after the IMP intake and which stopped after IMP intake of study drug (including medications and treatments which stopped the day of the IMP intake) will be considered as concomitant medications. If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of IMP dosing. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the IMP dosing. If there is clear evidence to suggest that the medication stopped prior to the IMP dosing, the medication will be assumed to be Prior.

Medications and treatments with a start date after the last dose of IMP will be considered as post-study medication and will not be considered as concomitant medications.

Concomitant medications will be analysed for arm A and arm B for the FAS.

The number (n) and percentage (%) of patients taking concomitant medications will be summarized by ATC classification and Preferred Name. ATC Level 1 will be sorted by alphabetical order. Preferred Names, within each ATC Level 1, will be sorted by descending frequency of the total frequency. In the event of Preferred Names with equal total frequencies, the relevant Preferred Names will be sorted alphabetically. Similarly, if a patient reported more than one concomitant or post-treatment medication within the same primary ATC Level 1, the patient will be counted only once.

Prior and concomitant medications (ATC Level 1/ Preferred Name), dose, frequency and route, start/stop date (or ongoing) and type of indication as specified in the eCRF with medication category (Prior or Concomitant) will be presented in the by- patient data listing for FAS.

Additional summaries and listing will be created specifically for Prior anti-cancer therapies.

4.9 Prior and Concomitant Radiotherapy and Procedure

Prior and concomitant radiotherapy will be summarized and listed for the FAS.

The following prior radiotherapy variables will be described:

- Number of patients having a history of radiotherapy
- Intent of prior radiotherapy
- Sites of prior radiotherapy

The following concomitant radiotherapy variables will be described:

- Number of patients having a concomitant radiotherapy
- Intent of concomitant radiotherapy
- Sites of concomitant radiotherapy

Concomitant procedure will be listed for the FAS.

4.10 Extent of Exposure

FAS population set will be considered for the analysis. Extent of exposure will be summarized for arm A and arm B. The below derived parameters will be listed by arm and patient.

4.10.1 RXC004

Duration and compliance of the RXC004 exposure will be assessed by computing the following variables:

- Number of cycles and number of doses per patient
- RXC004 Duration of treatment (weeks) = (Date of last dose – Date of first dose + 1) / 7
- Cumulative dose (mg) = Sum of all doses administered
- RXC0004 RDI (%) = [Cumulative dose received (mg) / (RXC004 Duration of treatment (days) * 2mg)] * 100, for Arm A
- RXC0004 RDI (%) = [Cumulative dose received (mg) / (RXC004 Duration of treatment (days) * 1.5mg)] * 100, for Arm A combination and Arm B

For switching patients in arm A, RXC0004 RDI for Arm A combination should be considered from the start of the combination.

- Number of patients with dose reduced and reason for reduction
- Number of patients with dose interrupted and reason for interruption

Duration of the RXC004 duration, and Cumulative dose will be summarized as continuous variables. RDI will be summarized as continuous variable and by categories:] - ; 60%[, [60% ; 75%[, [75% ; 90%[, [90% ; 100%],] 100% ; + [).

The number of patients who had dose reductions will be summarized by categories: (Any, 1, 2 times).

Another summary will be produced excluding treatment cycles after the progression for the patients who remain on treatment despite PD. A swimmer plot will be produced presenting the duration of treatment. A tag will show the first PD and when patients achieve response. For the patients in arm A who switched to combination, a different colour will be used for the monotherapy and the combination treatment. Swimmer plots will be presented separately for arm A and arm B

4.10.2 Nivolumab

Duration and compliance of the Nivolumab exposure will be assessed by computing the following variables:

- Number of cycles and number of doses per patient
- Nivolumab Duration of treatment (weeks) = (Date of last dose – Date of first dose + 28) / 7
- Cumulative dose (mg) = Sum of all doses administered
- Nivolumab RDI (%) = [(Cumulative dose received (mg) * 4 (weeks)) / (Nivolumab Duration of treatment (weeks) * 480 (mg))] * 100
- Number of patients with dose interruption and reasons for interruption
- Number of patients with dose delay and reasons for delay

Duration of the Nivolumab duration, and Cumulative dose will be summarized as continuous variables. RDI will be summarized as continuous variable and by categories:] - ; 60%[, [60% ; 75%[, [75% ; 90%[, [90% ; 100%],] 100% ; + [).

The number of patients who had dose reduction/delay will be summarized by categories: (Any, 1, 2, 3+ times).

Another summary will be produced excluding treatment cycles after the progression for the patients that remain on treatment despite PD.

4.11 Efficacy Evaluation

4.11.1 Analysis and Data Conventions

The statistical hypotheses for testing the activity of monotherapy and the combination independently are:

$$H0: p \leq p0$$

$$H1: p \geq p1$$

Where H0 is the null hypothesis, p is the observed response rate, p0 is the response rate for available treatment options – CCI [redacted], H1 is the alternative hypothesis and p1 is the target response rate – CCI [redacted]. For RXC004 monotherapy the primary summary measure is the DCR and the corresponding p0 and p1 are CCI% and CCI%. For the combination of RXC004 and nivolumab the primary summary measure is the ORR and the corresponding p0 and p1 are CCI% and CCI%.

4.11.1.1 Multi-centre Studies

There will not be any adjustment for study centres, subgroup analysis based on study centres are not planned.

4.11.1.2 Adjustments for Covariates

No statistical model will be provided for the analysis of study endpoints.

4.11.1.3 Handling of Dropouts or Missing Data

Missing data will not be imputed.

4.11.1.4 Multiple Comparisons/Multiplicity

Not applicable in this study.

4.11.1.5 Interim Analyses

There is no formal interim analysis planned

4.11.1.6 Examination of Subgroups

Not applicable in this study.

4.11.2 Primary Efficacy Variable(s)

All primary efficacy analyses will be conducted on the evaluable set.

Primary objective of study will consider the overall tumour response provided by Investigators. A listing containing information on target, non-target lesions, new lesions, overall response will be provided (ordered by arm, patient and visit).

4.11.2.1 Disease Control Rate (DCR)

The definition of DCR is provided in Section 3.2.1.3. DCR will be based on a individuals BOR using investigator RECIST 1.1 assessment. DCR is set as primary efficacy endpoint for arm A and secondary efficacy endpoint for arm B.

DCR and associated 90% confidence intervals (CIs), calculated using the Clopper Pearson method, will be summarized for arm A and arm B. For arm A, the patients who switched due to progression at first scan will be considered as having progressed. In addition, DCR will be summarized for arm A2 patients.

DCR will be listed for all patients in the evaluable set.

As an additional analysis, this analysis will be repeated considering the definition detailed in section 3.2.1.3.

4.11.2.2 Objective Response Rate (ORR)

Definition of ORR is provided in Section 3.2.1.3. ORR will be based on a individuals BOR using investigator RECIST 1.1 assessment. ORR is set as primary efficacy endpoint for arm B and secondary efficacy endpoint for arm A.

ORR and associated 90% CIs, calculated using the Clopper Pearson method, will be summarized for arm A and arm B. For arm A, the patients who switched due to progression at first scan will be considered as having progressed. In addition, ORR will be summarized for arm A2 patients.

BOR will be listed for all patients in the evaluable set

4.11.3 Secondary Efficacy Variables

All secondary efficacy analyses will be conducted on the FAS and, where appropriate, on the evaluable set.

4.11.3.1 Percentage change in sum of target lesions

The % change in sum of target lesions is defined in Section 3.2.1.4 .

Percentage change in tumour size will be derived at each visit by the percentage change from baseline in the sum of diameters of target lesions will be provided for arm A and arm B. It will also be summarized for arm A2.

In arm A and arm B, % change in sum of target lesions will be always computed considering screening sum of diameters as baseline. For patients in cluster arm A2, % change in sum of target lesion will be computed considering as reference the sum of diameters computed at Week 8. In case some individual lesions are not measured, the whole sum of target lesions will be considered as missing.

Percentage change in tumour size will be listed per visit for all patients in FAS.

The best percentage change in tumour size will be the patients value representing the largest decrease (or smallest increase) from baseline in tumour size.

A waterfall-plot will be produced to report the best % change in sum of target lesions for each patient (considering the minimum observed value) ordered by largest increase to greatest decrease. In addition, two waterfall-plot will be produced to report the % change in sum of target lesions at Week 8 and Week 16. Best overall responses (BOR) will be highlighted for each patient. The figure will be repeated considering RNF43 and RSPO2/3 Status instead of BOR.

A Spider-plot will be drawn to describe the % change in sum of target lesion. Vertical axis will represent the % change in sum of target lesions (% change in tumour size) while the horizontal axis will represent days from screening, as follows:

day (x-axis) = date of RECIST 1.1 assessment – first dose of study treatment (C0D1)

Best overall responses (BOR) will be highlighted for each patient. The figure will be repeated considering RNF43 and RSPO2/3 Status instead of BOR.

All plots will be provided for the FAS separately for arm A, arm A2 and arm B. The spider plot for A2 will still use the original baseline to week 8 so it is clear what the changes were when the patient switched to the combination.

4.11.3.2 Progression Free Survival (PFS)

PFS is defined in Section 3.2.1.5.

Kaplan-Meier analyses will be conducted for arm A and arm B (in the same plot) and separately for arm A2. For arm A, the patients who switched due to progression at first scan will be considered as having progressed. Survival plots will be produced to present Kaplan-Meier estimated curves. In

addition, the following parameters estimated from the Kaplan-Meier curves will be provided for each group:

- median PFS and corresponding 95% CIs
- PFS rate at 3, 6 and 12 months and corresponding 95% CIs (one month = 30.4375 days).

PFS will be listed for all patients in the FAS.

4.11.3.3 Overall Survival

OS is defined in Section 3.2.1.6.

Kaplan-Meier analyses will be conducted for arm A and arm B (in the same plot) and separately for arm A2. Survival plots will be produced to present Kaplan-Meier estimated curves.

OS will be listed for all patients in the FAS.

4.11.4 Pharmacokinetics/Pharmacodynamic

CCI [redacted]

4.12 Safety Evaluation

Safety summaries and analyses will be based on the FAS.

4.12.1 Adverse Events

Adverse Events will be collected from time of signature of informed consent form throughout the treatment period and until 30 days after the last dose of RXC004 (for patients treated with RXC004 monotherapy only) or 90 days after the last dose of Nivolumab (for patients treated with RXC004 and Nivolumab).

SAEs will be recorded from the time of signing of informed consent form until the follow-up period is completed: 30 days after the last dose of RXC004 (for patients treated with RXC004 monotherapy only) or 90 days after the last dose of Nivolumab (for patients treated with RXC004 and Nivolumab).

The following variables will be collected for each AE:

- AE (verbatim)
- Start/Stop date
- CTCAE grade at onset and grade changes
- Seriousness
- Investigator causality rating against the Investigational Product(s)
- Action taken with regard to Investigational Product(s)
- Action taken with regards to AE

- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Hospitalisation
- Life Threatening
- Congenital Anomaly or Birth Defect
- Disability or Permanent Damage
- Other Medically Important Serious Event
- Date of hospitalisation
- Date of discharge
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

Partially complete AE dates will not be imputed in the listings and the available day, month and year components will be used to determine if an adverse event is treatment- emergent taking the first dosing date last treatment date as references.

More specifically:

- Start date of AE missing: Assumed to be date of first treatment dose.
- Start day and month of AE missing: Assumed to be date of first treatment dose (if same year for both dates), January 1st otherwise.
- Start day of AE missing: Assumed to be date of first treatment dose (if same month and year for both dates), first day of the month otherwise.
- End date for non-ongoing AE missing: Assumed to date of last treatment dose
- End day and month for non-ongoing AE missing: Assumed to be date of last treatment dose (if same year for both dates), December 31st otherwise.
- End day for non-ongoing AE missing: Assumed to be date of last treatment dose (if same month and year for both dates), last day of the month otherwise.

Explain if first use TEAEs with missing relationship to the study drug will be considered as related.

AEs will be coded using the MedDRA, latest version. Grading will be performed using CTCAE version 5.0.

TEAEs are defined as those AEs with an onset after dosing and those pre-existing AEs that worsen after the start of dosing and within 30 days of stopping RXC004 monotherapy or 90 days after the last actual Nivolumab dose (for patients on RXC004 and Nivolumab combination).

An overview table of TEAEs will be provided showing the number of patients, the percentage of patients and the number of events for the following categories of events:

- Any TEAE
- Any treatment related TEAE to RXC004
- Any treatment related TEAE to Nivolumab
- Any grade >= 3 TEAE
- Any grade >= 3 TEAE related to RXC004
- Any grade >= 3 TEAE related to Nivolumab
- Any serious TEAE (STEAE)
- Any serious TEAE related to RXC004
- Any serious TEAE related to Nivolumab
- Any TEAE leading to death
- Any TEAE leading to permanent discontinuation or reduction or interruption of RXC004
- Any TEAE leading to permanent discontinuation of RXC004
- Any TEAEs leading to RXC004 reduction
- Any TEAEs leading to RXC004 interruption
- Any TEAE leading to permanent discontinuation or interruption of Nivolumab
- Any TEAE leading to permanent discontinuation of Nivolumab
- Any TEAEs leading to Nivolumab interruption

For TEAEs, TEAEs considered related (RXC004 and Nivolumab), STEAEs, STEAEs considered related (RXC004 and Nivolumab), TEAEs leading to study treatment discontinuation, TEAEs leading to RXC004 reduction, TEAEs leading to RXC004 interruption, TEAEs leading to Nivolumab interruption, TEAEs by maximum grade, TEAEs with grade >=3, TEAEs with grade >=3 related to RXC004, TEAEs with grade >=3 related to Nivolumab, death, detailed tables will be created showing the number of patients who experienced at least one TEAE, the corresponding percentage of patients and the number of events by SOC and PT.

SOC will be sorted by alphabetical order. PTs, within each SOC, will be sorted by descending order of total frequency. In the event of PTs with equal total frequencies, the relevant PTs will be sorted

alphabetically.. In addition, a table summarizing TEAEs by decreasing frequency of Preferred Terms will be produced for all TEAEs and TEAEs related to RXC004/Nivolumab.

A table will also be produced showing the details for every patient that die (death date, cause of death etc…).

Listing of all AEs (including non-treatment-emergent events) will be provided. This listing will be presented, ordered by arm and patient. It will include patient identifier, AE (SOC, PT, and verbatim term), date of onset, date of resolution, duration, maximum grade, seriousness, action taken, outcome and causality. A listing detailing the serious TEAEs will also be produced.

TEAEs summaries will be conducted for arm A and arm B and separately for arm A1 and arm A2 (in the same table) as applicable.

4.12.2 Dysgeusia

Loss of taste (dysgeusia) is an on-target adverse event known to occur with porcupine inhibition. A taste assessment questionnaire will be performed at screening and at each study visit when patient reports dysgeusia.

A bar-chart will present the worst answers to the main questions after screening and a separate one illustrating the worst answers on the way the taste is altered. In the event a patient answering in both directions of 'more sensitive' or 'loss' then loss will be considered worse. A by-patient listing will also be provided.

4.12.3 Clinical Laboratory Evaluation

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the SoA (see protocol). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the eCRF.

The clinical chemistry and haematology will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

In case of BLQ values (eg "<5", "<100") for some assessments, the following rule will be considered:

- If less than 50% of the assessments (across patients) are BLQ such as "<XXX", then "XXX/2" will be considered for summaries.

- If 50% or more than 50% of assessments (across patients) are BLQ such as "<XXX" then "0" will be considered for summaries.

The following laboratory variables will be measured:

- Haematology (whole blood): Haemoglobin (Hb), Lymphocytes (absolute count and %), Neutrophils (absolute count and %), Platelet count, Total white cell count. , .
- Clinical Chemistry (serum or plasma): Albumin, Alanine transaminase (ALT), Alkaline phosphatase (ALP), Amylase (only for arm B), Aspartate transaminase (AST), Calcium, Calcium corrected, Creatinine, CRP, Glucose, Lactate dehydrogenase (LDH), Lipase (only for arm B), Magnesium, Phosphate, Potassium, Sodium, Total bilirubin, Urea. .

The original lab test units will be converted using the International System of Units (SI) [11].

Laboratory test with numerical grading criteria in the NCI CTCAE v5.0 will be graded accordingly. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE v5.0 results will be classified as low, normal or high based on laboratory normal ranges.

The following summaries will be provided for all parameters for arm A and arm B:

- A summary of results by assessment visit (as per SoA)
- Shift tables will be provided for all parameters to compare a patient's baseline laboratory grade relative to worst post-baseline grade (Low and/or High abnormal direction will be considered for each parameter).

By-patient listing will be provided for all patient in FAS by arm and visit, including changes from baseline, grade and reference range. All values outside the clinical reference ranges will also be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range. In addition, box plots presenting the results per visit will be presented for each lab parameters.

eDISH plots will also be produced to assess the liver toxicity.

4.12.4 Vital Signs, Physical Examinations and Other Observations Related to Safety

4.12.4.1 Vital Signs

The following vital signs will be recorded at baseline and post-baseline visit:

- Weight (kg)
- Systolic blood pressure (in mmHg)

- Diastolic blood pressure (in mmHg)
- Pulse rate (beats/minute)
- Temperature (°C or °F)
- Respiratory rate (breaths per minute)

A shift table from baseline systolic blood pressure and diastolic blood to worst on-treatment results will be presented. The normal/abnormal classification will be made using the criteria defined in table below:

Table 2 – Vital Sign Criteria for Abnormalities

Vital Sign Criteria for Abnormalities	**Criteria for Abnormalities (any of the following situation)**
Systolic blood pressure	- value <80 mmHg - value >129 mmHg
Diastolic blood pressure	- value <60 mmHg - value >80 mmHg

Vital signs data and clinically relevant abnormalities in vital signs will also be listed.

4.12.4.1 CCI [redacted]

Blood samples for CCI will be obtained from patients at timepoints specified in the SoA. Summary statistics of values and relative change from baseline by visit will be presented for CCI values. By-patient listing will be provided for all patient in FAS by visit, including values and changes from baseline.

4.12.4.2 Electrocardiograms (ECG)

Triplicate 12-lead ECGs will be performed at timepoints as specified in the SoA (see protocol). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. Mean QT intervals corrected for heart rate should be calculated using Fridericia's formula (QTcF). The following variables will be collected:

- PR Interval (msec)
- RR Interval (msec)
- QRS Complex (msec)
- QT Interval (msec)
- QTcF interval (msec)

Mean of the 3 measures (considering 1 decimal) will be considered at each timepoint (Pre-dose, 1-hour dose, 12-hour dose).

ECGs will be performed 3 times and an overall evaluation will be provided, as follows:

- Overall ECG evaluation (normal, abnormal – not clinically significant, abnormal – clinically significant)

A shift table of baseline QTcF to worst on-treatment results will be presented. For rating the worst on-treatment value, the following categories will be used based on the varying degrees of abnormality above, in the order of least to most severe (top to bottom):

- Missing result
- <=450 msec (i.e. 'normal')
- >450-<=480 msec
- >480-<=500 msec
- >500 msec

Baseline QTcF will be the pre-dose value at baseline. Worst on-treatment QTcF will be the worst post-baseline all timepoints considered.

All ECG parameters will be listed.

4.12.4.3 Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be assessed at the times specified in the SoA based on the following (see protocol):

0. Fully active; able to carry out all usual activities without restrictions
1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g. light housework or office work)
2. Ambulatory and capable of 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; unable to carry out any self-care and totally confined to bed or chair

5 Dead

A shift table will be presented to show worst changes from baseline separately for arm A and arm B. ECOG score results (including screening value) will be listed by arm and visit.

4.12.4.4 Bones Evaluation

Blood Sample for CCI [redacted] and DXA scan assessments will be performed at timepoints as specified in the SoA (see protocol). The following variables will be collected:

- CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Bones Evaluation variables will also be listed.

CCI [redacted]

4.12.4.5 Physical Examination

Physical Examination will be assessed at the times specified in the SoA. By-patient listing will be provided for all patient in FAS by visit, including details in abnormalities if any.

4.12.5 Safety Monitoring Committee

A safety monitoring committee (SMC) will be appointed to review safety data from patients in this study and a second study of RXC004 in patients with pancreatic and biliary tract cancer (RXC004/0003).

The SMC is a group consisting of the country principal investigators (PI) from each of the phase 2 studies and a statistician. An independent bone metabolism consultant will review the data and provide expert advice to the SMC meetings, but will not be a formal member of the SMC.

The SMC will be convened to review the safety and tolerability of RXC004 at regular intervals.

The safety reviews will start when approximately [redacted] patients across the phase 2 clinical trial program have been dosed for at least 1 cycle of study treatment and will continue every 6 months until the phase 2 studies close or last patient discontinues study treatment (whichever occurs first). Additional safety reviews may be performed at other times as deemed appropriate by the Sponsor.

Since the studies are open label, there are no blinding issues associated with performing interim safety reviews. Full details of the SMC procedures, processes, and analyses can be found in the SMC Charter.

4.13 Exploratory Objectives

CCI [redacted]

4.14 Determination of Sample Size

The method by Frewer et al [10], together with the totality of the data collected, will be used to guide go/no-go decision making:

For the combination RXC004+nivolumab arm, assuming a CCI [redacted]% response rate which is considered to be clinically significant in the target population, against a reference value of CCI [redacted]% response rate (Eng C et al 2019) as CCI [redacted], then a sample size of 20 achieves greater than CCI [redacted]% power, at the CCI [redacted] CCI [redacted] CCI [redacted] These hurdles will be used to guide the decision for onward development. The totality of the data, including the results from the secondary endpoints will be used to in the final decision.

For the monotherapy RXC004 arm, assuming a CCI [redacted]% disease control rate which is considered to be clinically significant in the target population, against a reference value of CCI [redacted]% DCR [11 - 12] as a CCI [redacted], then a sample size of 20 achieves greater than CCI [redacted]% power, at the CCI [redacted] CCI [redacted] CCI [redacted] These hurdles will be used to guide the decision for onward development. The totality of the data, including the results from the secondary endpoints will be used to in the final decision.

Approximately CCI [redacted] patients are expected to be enrolled in order for approximately 20 patients to be in the evaluable dataset in each treatment arm.

4.15 Changes in the Conduct of the Study or Planned Analysis

In order to make the most appropriate assessment of efficacy for the compound and not be influenced by early dropouts not due to drug the Evaluable set will require at least 4 weeks of RXC004 intake

and at least one post dose radiographic tumour assessment or progressed/died ahead of the first radiographic assessment instead of one single dose as initially planned.

After an ongoing review of the available data the following changes to the final outputs were made compared to the protocol

- Medical History will not be summarized but will be listed.
- CCI
- Overall Survival will not be summarized but will be listed.

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6 APPENDICES

6.1 Anti-Tumour Activity assessment

The anti-tumour activity of RXC004 monotherapy and RXC004+Nivolumab will be assessed by investigator at site by utilizing images from explain (CT) or explain (MRI), collected during screening/baseline and at regular (follow-up) intervals during the study. It is important to follow the tumour assessment schedule as per the SoA (see protocol). Patients treated with RXC004+Nivolumab that continue after RECIST 1.1 progression, will continue tumour assessment until second RECIST 1.1 defined radiological progression (relative to the initial RCX004+Nivolumab progression event).

Tumour assessments utilize images from CT or MRI, collected during screening/baseline and at regular (follow-up) intervals during the study. Tumour assessments will continue until RECIST 1.1-defined radiological progression. Patients treated with RXC004+Nivolumab that continue treatment after RECIST 1.1 progression, will continue tumour assessments until second RECIST 1.1 defined radiological progression (relative to the initial RXC004+Nivolumab progression event).

Sites will be required to store electronic copies of all scans, and the Sponsor may arrange for possible centralised storage of all imaging data. Centralised storage of imaging data would be possible to support an independent centralized review of disease assessments.

At baseline, tumour lesions/lymph nodes will be categorized in measurable or non-measurable as follows:

- *Measurable tumour 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 CT scan (CT scan slice thickness no greater than 5 mm).
- *Measurable malignant lymph nodes*: to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- *Non-measurable*: 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 non-measurable lesions.

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to

reproducible repeated measurements. All other lesions including pathological lymph nodes should be identified as non-target lesions.

At each tumour assessment visit, the sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions in mm) for all target lesions will be calculated. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum.

The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease. The minimum observed sum of diameters is called "Nadir" and this includes the baseline sum if that is the smallest observed on study. If a lesion split into different components, it will be considered as single lesion where the diameter is obtained by the some of the longest diameter of each single component.

RECIST 1.1 guideline will be followed to determine the overall tumour response based on target lesions, non-target and new lesions responses. Tumour assessment visits will be conducted, in accordance with SoA (see protocol), every 8 weeks ± 1 week (relative to the date of initiation of study treatment) for the first 56 weeks, followed by q12w weeks ± 1 until radiological disease progression (as defined by Response Evaluation Criteria in Solid Tumours, version 1.1 [RECIST 1.1]).

6.1.1 Target Lesions (TLs) assessment

At each tumour assessment visit, the response for TLs will be determined as follows:

- *Complete response (CR):* disappearance of all target lesions i.e. explain (SLD) = 0. However, a CR can be achieved with SLD >0 if a pathological lymph node is identified as a target lesion and has a reduction in short axis to <10 mm.
- *Partial response (PR):* A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive disease (PD):* at least a 20% increase in the sum of diameters of target lesions, taking as reference the nadir. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- *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.
- *Not all evaluated:* if one or more than individual lesions is missing, the sum of longest diameters is also missing, nevertheless the available sum meets criteria for PD.

6.1.2 Non-Target Lesions (NTLs) assessment

At each tumour assessment visit, each NTL will be evaluated as follows:

- *Complete Response (CR)*: Disappearance of all NTLs. All lymph nodes must be non-pathological in size (<10 mm short axis).
- *Non-CR/Non-PD*: Persistence of one or more NTLs and/or maintenance of tumour marker level above the normal limits.
- *Progressive Disease (PD)*: Unequivocal progression of existing NTLs.

6.1.3 New Lesions (NLs) assessment

The presence of new measurable lesions and new non-measurable lesions will be assessed at each tumour assessment visit (after baseline). The occurrence of NLs will be recorded as dichotomous response "Yes" or "No". New measurable/non-measurable lesions will be assessed in accordance to baseline criteria for identification of measurable/non-measurable lesions. NLs identified in lymph nodes will be considered only if lymph node is ≥15 mm in short axis.

6.1.4 Overall Response (OR)

At each tumour assessment visit, OR will be determined as defined in the RECIST 1.1 guideline. Table 3 shows rules to determine the OR outcome. For example, if a patient resulted in PR for TLs, not-evaluated for NTLs and without NLs ("No"), the overall response at the considered visit will be PR.

Table 3 - Time point response: patients with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	**CR**
CR	Non-CR/non-PD	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**

(CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and, NE = not-evaluable)

Furthermore, PD can be also considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis from the primary cancer under study should be considered as disease progression and

not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.2 Summary of treatment arms to be considered for each endpoint

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Endpoints	Arms to consider
DCR	Arm A/B and arm A2
ORR	Arm A/B and arm A2
PFS	Arm A/B and arm A2
Percentage change in tumor size	Arm A/B and Arm A2
AEs	Arm A/B and Arm A1/A2
Rest of endpoints	Arm A/B unless otherwise specified

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