Cover page

Document title: A Modular, Phase II, Open-Label, Multicentre Study to Assess the Preliminary Efficacy and Safety of RXC004, in Patients with Advanced Solid Tumours that have Progressed following Therapy with Current Standard of Care

NCT number: NCT04907851

Date of the Document: 15 February 2024

Parexel International

Redx Pharma Plc

RXC004/0003

A Modular, Phase II, Open-Label, Multicentre Study to Assess the Preliminary Efficacy and Safety of RXC004, in Patients with Advanced Solid Tumours that have Progressed following Therapy with Current Standard of Care

Statistical Analysis Plan

Version: 4.0

Parexel Project Number: 255172

SPONSOR SIGNATURE PAGE

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

	Signatories
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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 on the final page by the following:

	Signatories
Author	PPD Project Role: PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	22-Jul-2021	New document
2.0	25-Jan-2022	SMC meeting Revision of Adverse Events section (Outputs added, AEPI, Dysgeusia assessment) Add CCI [redacted] Add eDISH plots Add Dysgeusia evaluation
3.0	21-Sep-2023	Add new variables in Baseline Characteristics Revision of RDI definitions Revision of sorting rules for AEs and ConMeds Add CCI [redacted] analysis
4.0	15-Feb-2024	Revision Objectives endpoints definition Revision Evaluable Set definition Revision Concomitant Medications imputation rules Add CCI [redacted] 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
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-inf})}$	AUC from time zero extrapolated to infinity
CCI	CCI
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent clearance following oral administration
CRF	Case Report Form
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration in the dosing interval
DBP	Diastolic blood pressure
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EoS	End-of-study
CCI	CCI
HR	Heart rate
ICF	Informed consent form
IMP	Investigational Medicinal Product
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not available
NK	Not known
PFS	Progression-free survival
PK	Pharmacokinetic

Abbreviation/Acronym	Definition/Expansion
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
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to occurrence of C_{max}
WHO-DD	World Health Organisation - Drug Dictionary
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 6 (04-Jan-2023)
- electronic Case Report Form (eCRF), Version 4.0 (01-Aug-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.

CCI [redacted]
CCI [redacted]

2 STUDY OBJECTIVES

Objectives	Endpoints
Primary	
To assess the anti-tumour activity of RXC004	• Monotherapy (Modules 1 and 2): PFS rate (%) at 6 months using investigator assessment according to RECIST 1.1 • Combination therapy (Module 3): Objective response rate (ORR) using each patient's BOR according to RECIST 1.1
Secondary	
To further assess the preliminary efficacy of RXC004	• Monotherapy (Modules 1 and 2): Objective Response Rate (ORR), Disease Control Rate (DCR), PFS and % change in the sum of target lesions using investigator assessments according to RECIST 1.1, and overall survival (OS) • Combination therapy (Module 3): DCR, PFS and % change in the sum of target lesions using investigator assessments according to RECIST 1.1, and OS.
To assess the PK of RXC004	Maximum plasma concentration (Cmax) after Dose 1, Cmax at steady state, minimum observed plasma concentration (Cmin) at steady state as well as other

Objectives	Endpoints
	relevant parameters (e.g. tmax, t½, λz, AUC0-∞, CL/F, and Vz/F).
Safety	
To assess the safety and tolerability profile of RXC004	Incidence of adverse events (AEs), serious adverse events (SAEs), dose reductions, interruptions, discontinuation and assessment of dysgeusia
Exploratory	
CCI	• CCI
CCI	• CCI
CCI	• CCI
CCI	• CCI
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Objectives	Endpoints
CCI CCI	• CCI CCI CCI

1 Evaluated using Investigator assessments according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

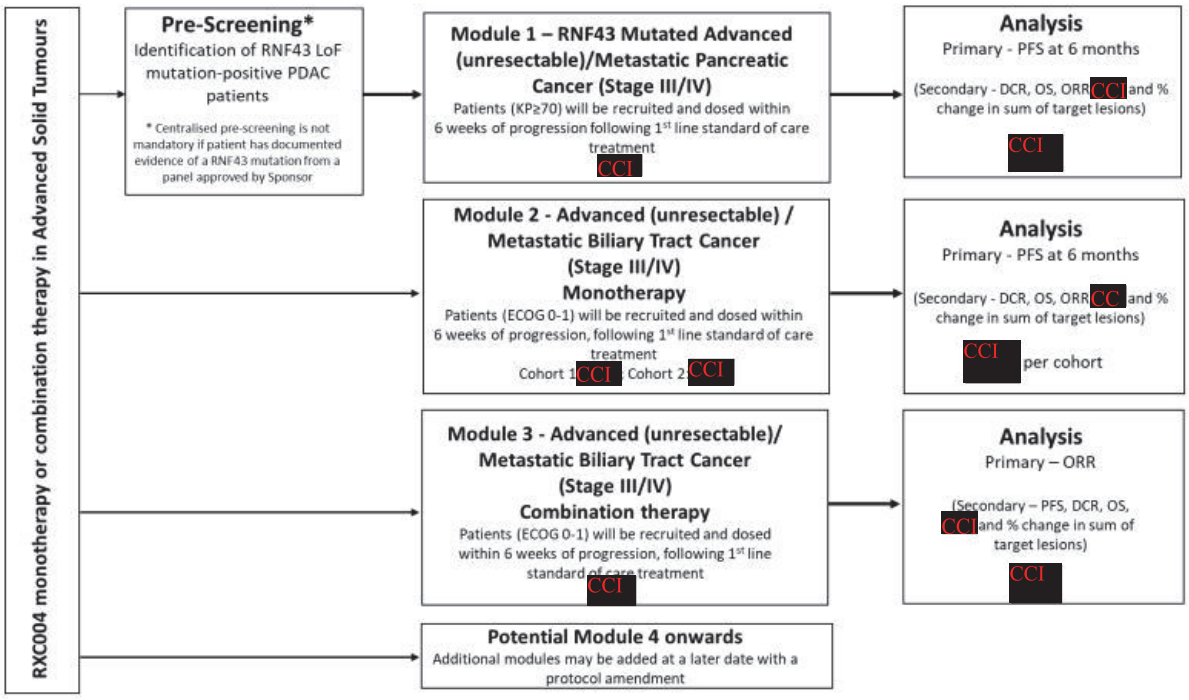
This is Phase II, modular, open label, multicentre, study to evaluate the preliminary efficacy and safety of RXC004 monotherapy in advanced solid tumours that have progressed following standard of care treatment.

The study initially opened with ring finger protein 43 (RNF43) loss of function (LoF) mutation-positive pancreatic ductal adenocarcinoma (PDAC) (Module 1) and biliary tract cancers (BTC) (Module 2). The purpose of Module 3 is to evaluate RXC004 1.5 mg in combination with pembrolizumab in patients with BTC. CCI evaluable patients will be enrolled in each module.

The primary objective of the study is to assess the preliminary efficacy of RXC004 in each module in terms of progression free survival (PFS) at 6 months. Tumour assessment will be performed by Investigators every 6 weeks ± 1 week (relative to the date of initiation of study treatment) for the first 54 weeks, followed by q12w ± 1 week until radiological disease progression (as defined by Response Evaluation Criteria in Solid Tumours, version 1.1 [RECIST 1.1]). 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, CCI ECOG performance status, LoF, Loss of Function, ORR objective response rate; OS Overall survival; PFS progression free survival; KP Karnofsky performance status; RNF43 Ring finger 43; RXC004 Porcupine inhibitor.

The analyses will be conducted independently for each module. The module data will be locked before their analyses. All the populations and endpoints described hereafter must be considered independently for each module.

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 66):
  - PFS
  - 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
  - CCI
  - CCI

- Overall Survival (OS)

In case the RECIST 1.1 assessment will be done across several days:

- The first day of assessment will be considered in case of progressive disease (PD) as overall response (OR).
- The last day of assessment will be considered in case of response (complete response [CR], partial response [PR] or stable disease [SD]) as OR.

3.2.1.1 Progression Free Survival

PFS is defined as the time from first dose of study treatment (C0D1) until the date of disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdraws from the assigned study treatment or receives another anticancer treatment 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>=12 +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 12 + 1 weeks from first dose date without a post baseline scan) then its death date will be treated as their progression date. Progression free survival rate at 6 months is the primary endpoint. 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

Progression free survival rate at 6 months will be defined as the proportion of patients alive and progression free at 6 months.

3.2.1.2 Best Overall Response

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).

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 6 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 5 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.

3.2.1.3 Objective Response Rate

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. Responses on subsequent treatments after discontinuing will not be included.

3.2.1.4 Disease Control Rate

DCR is defined as the proportion of patients with a BOR of either CR, PR or SD for at least 6 weeks post-baseline (corresponding to SD for 1 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 6 visit will be applied such that any scan that is at least 5 weeks after starting treatment will considered acceptable for the evaluation of response.

3.2.1.5 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

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.

3.2.1.6 CCI

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3.2.1.7 CCI

CCI

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CCI

3.2.1.8 Overall Survival

OS is defined as the time from the first day of study treatment (C0D1) 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 time is defined as:

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

3.2.2 Pharmacokinetic Variables

CCI [redacted]

3.2.3 Safety Variables

The following safety variables will be evaluated:

- AEs and SAEs
- Dysgeusia
- Vital signs
- 12-lead Electrocardiogram (ECG)
- ECOG or KP performance status
- Prior and concomitant medications
- Clinical laboratory evaluation
- CCI [redacted]

3.2.4 Tertiary Endpoint

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

3.2.5 Exploratory Variables

CCI [redacted]

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 (SOP).

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.

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 18)
Day 22	(Day 19 - Day 32)
Day 43	(Day 33 - Day 53)
Day 64	(Day 54 - Day 74)
Day 85	(Day 75 - Day 95)
Day 106	(Day 96 - Day 116)
Day 127	(Day 117 - Day 137)
Day 148	(Day 138 - Day 158)
Day 169	(Day 159 - Day 179)
Day 190	(Day 180 - Day 200)
Day 211	(Day 201 - Day 221)
Day 232	(Day 222 - Day 242)
Day 253	(Day 243 - Day 263)
Day 274	(Day 264 - Day 284)
Day 295	(Day 285 - Day 305)
Day 316	(Day 306 - Day 326)
Day 337	(Day 327 - Day 347)
Day 358	(Day 348 - Day 368)

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.

4.2.4 End of Study (EoS)

A patient 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 EoS 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). The study data is planned to be analysed and reported based on all patient data at the primary completion data cut-off date (approximately 24 weeks after cycle 1 day 1 for the last patient in), or at the End of Study, whichever comes first.

4.2.5 Data Listings

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 separately for module 1 and module 2&3.

4.2.7 Figures

Figures will be presented independently for each module.

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, 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

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

The following summaries will be provided:

- A summary of the number of patients who were screened (who signed main study ICF), who were exposed to study treatment, who completed the study or discontinued and primary reason for end of treatment will be summarized in the FAS.
- A summary of 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.

4.4.1 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 patient's rights, safety, or well-being; and/or on the validity of the data for analysis. Protocol deviations are defined in the project-specific Protocol Deviation Specification. Whether a protocol deviation result 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 each Module 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. Percentage of patients 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 were enrolled and received at least one dose of study drug (RXC004).
- 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.

The following demographic variables will be described:

- 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)

The following baseline characteristic variables will be described:

- Weight (kg)
- Height (only screening visit) (cm)
- Body mass index (BMI) (kg/m^2)
- ECOG Performance Status at Study Entry (Modules 2&3 only)
- Karnofsky Performance Status at Study Entry (Module 1 only)
- Albumin at Study Entry
- Stage at Study entry
- Primary Location
- Cancer Classification (Histology)
- Histological Grade
- TNM Status
- RNF43 Status (Module 1 only)
- 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 (as per extent of disease form)
- Number of Prior Lines of Cancer Therapy
- Best Response Achieved for the Most Recent Treatment Prior to Study Entry
- 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 using the rules above) 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 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 Treatment Exposure/Compliance

Treatment Exposure

Duration and compliance of the RXC004 exposure will be assessed by computing the following variables from RXC0004 Drug Administration form:

- Number of cycles and number of doses per patient
- RXC004 Duration of treatment (weeks) = (Date of last dose – Date of first dose + 1) / 7
- Pembrolizumab Duration of treatment (weeks) = (Date of last dose + 42 – Date of first dose) / 7
- Cumulative dose (mg) = Sum of all doses administered
- RXC0004 RDI (%) = [Cumulative dose received (mg) / (RXC004 Duration of treatment (days) * 2mg)] * 100, for Module 1&2
- RXC0004 RDI (%)= [Cumulative dose received (mg) / (RXC004 Duration of treatment (days) * 1.5mg)] * 100, for Module 3

- Pembrolizumab RDI (%) = [(Cumulative dose received (mg) * 6 (weeks)) / (Pembrolizumab Duration of treatment (weeks) * 400 (mg))] * 100, for Module 3
- 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: [0%; 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. Some tags will show the RECIST assessment responses (CR, PR, SD, PD) along the study.

4.11 Efficacy Evaluation

4.11.1 Analysis and Data Conventions

The statistical hypotheses for testing the activity of RXC004 in module 1 (pancreatic cancer) and module 2 (biliary tract cancer) independently are:

H_0: $p \leq p0$

H_1: $p \geq p1$

Where H_0 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].

The primary summary measure is the progression free survival rate at 6 months. For module 1 the corresponding p0 and p1 are CCI [redacted]% and CCI [redacted]%. For module 2 the corresponding p0 and p1 are CCI [redacted]% and CCI [redacted]%.

4.11.1.1 Multi-center 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)

Primary efficacy analyses will be conducted on the FAS. A listing containing information on target, non-target lesions, new lesions, overall response will be provided (ordered by patient and visit).

4.11.2.1 Progression Free Survival

PFS is defined in Section 3.2.1.1.

Kaplan-Meier analyses will be conducted for each module. 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 90% CIs and 95% CI (one month = 30.4375 days).

PFS will be listed for all patients in the FAS.

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 Objective Response Rate

Definition of ORR is provided in Section 3.2.1.3. ORR will be based on a individuals BOR using the Investigator RECIST 1.1 assessment.

ORR and associated 90% CIs, calculated using the Clopper Pearson method, will be summarized for FAS and evaluable set.

BOR will be listed for all patients in the FAS.

4.11.3.1 Disease Control Rate

The definition of DCR is provided in Section 3.2.1.4. DCR will be based on a individuals BOR using the Investigator RECIST 1.1 assessment.

DCR and associated 90% CIs, calculated using the Clopper Pearson method, will be summarized for the FAS and evaluable set.

4.11.3.1 Percentage change in sum of target lesions

The % change in sum of target lesions is defined in Section 3.2.1.5 .

Percentage change in tumour size will be derived at each scan assessment by the percentage change from baseline in the sum of diameters of target lesions and will be provided for the FAS. In case some individual lesions are not measured, the whole sum of target lesions will be considered as missing.

% change in sum of target lesions will be always computed considering screening sum of diameters as baseline.

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.

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 baseline, as follows:

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

All plots will be provided for the FAS.

4.11.3.2 Overall Survival

OS is defined in Section 3.2.1.8.

Kaplan-Meier analyses will be conducted on the FAS. 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

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4.12 Safety Evaluation

Safety summaries and analyses will be based on the FAS as defined in Section 4.5.

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.

SAEs will be recorded from the time of signing of main study informed consent form until the follow-up period is completed: 30 days after the last dose of RXC004for patients treated with RXC004 monotherapy only) or 90 days after the last dose of Pembrolizumab (for patients treated with RXC004 and Pembrolizumab).

The following variables will be collected for each AE:

- AE (verbatim)
- Start/Stop date
- NCI 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

- Death
- 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 and 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 first 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.

Treatment-emergent adverse events (TEAEs) with missing relationship to the study drug will be considered as related.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), latest version.

Grading will be performed using NCI 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.

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 serious TEAE (STEAE)
- Any treatment related TEAE
- Any serious TEAE related
- Any TEAE leading to permanent discontinuation of RXC004
- Any TEAEs leading to RXC004 reduction
- Any TEAEs leading to RXC004 interruption

For TEAEs, TEAEs considered related, STEAEs, STEAEs considered related, TEAEs leading to study treatment discontinuation, TEAEs leading to RXC004 reduction, TEAEs leading to RXC004 interruption, TEAEs by maximum grade, TEAEs with grade >=3, TEAEs with grade >=3 related, 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.

For module 1 and 2, AE relatedness corresponds to a relation to RXC004. For Module 3, AE relatedness corresponds to at least one of RXC004/pembrolizumab relation.

For all AE summaries, 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.

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 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.

In addition, data related to dysgeusia examination questionnaire will be listed. The data will also be summarized as categorical data providing there are enough data to make it meaningful to do so.

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, Aspartate transaminase (AST), Calcium, Calcium corrected, Creatinine, CRP, Glucose, Lactate dehydrogenase (LDH), Lipase, Magnesium, Phosphate, Potassium, Sodium, Total bilirubin, Urea.

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

Laboratory test with numerical grading criteria in the NCI CTCAE version 5.0 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 NCI CTCAE version 5.0 results will be classified as low, normal or high based on laboratory normal ranges.

The following summaries will be provided for all parameters:

- Summary statistics of values and absolute change from baseline by 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 visit, including values, 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 parameter.

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)
- Temperature (°C or °F)
- Systolic blood pressure (in mmHg)
- Diastolic blood pressure (in mmHg)
- Pulse rate (beats/minute)
- Respiratory rate (breaths per minute)
- BMI
- O2 Saturation

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.

4.12.4.2 CCI

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4.12.4.3 Electrocardiograms

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 recorded:

- PR interval (msec)
- RR interval (msec) – In case RR is not recorded, then RR will be calculated as 60/HR.
- 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.

4.12.4.4 Karnofsky Performance Status - **Module 1 only**

Karrnofsky performance status will be assessed at the times specified in the SoA based on the following (see protocol) **for module 1**:

100. Normal no complaints
90. Able to carry on normal activities. Minor signs or symptoms of disease
80. Normal activity with effort
70. Care for self. Unable to carry on normal activity or to do active work
60. Requires occasional assistance, but able to care for most of his/her needs
50. Requires occasional assistance and frequent medical care
40. Disabled. Requires special care and assistance
30. Severely disabled. Hospitalisation indicted though death non-imminent
20. Very sick. Hospitalisation necessary. Active supportive treatment necessary
10. Moribund

A shift table will be presented to show worst changes from baseline. Karnofsky score results will be listed by visit.

4.12.4.5 Eastern Cooperative Oncology Group Performance Status (ECOG) - **Module 2&3 only**

ECOG performance status will be assessed **for module 2&3** 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. ECOG score results (including screening value) will be listed by visit.

4.12.4.6 Bone Evaluation

Blood Sample for Bone Turnover Biomarkers (beta C-terminal cross-linked telopeptide of type I collagen [b-CTX]) and dual-energy x-ray absorptiometry (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]

CCI [redacted]

4.12.4.7 Bones Evaluation variables will also be listed. 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 parallel study in CRC. 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 first data review meeting will be scheduled to occur when approximately CCI patients have received at least 1 cycle of treatment across the two studies and subsequent meetings will be held 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 or SMC.

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 Tertiary Analyses

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4.14 Exploratory Analyses

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4.15 Determination of Sample Size

The method by Frewer et al (**Error! Reference source not found.**), together with the totality of the data collected, will be used to guide go/no-go decision making:

Module 1

For the population under investigation, the standard of care of liposomal irinotecan in combination with 5-FU/Leucovorin reported a 6 month PFS rate of CCI% (NAPOLI-1 trial, **Error! Reference source not found.**). This level of CCI% will be the CCI. An improvement to CCI% in 6 month PFS rate would be considered clinically significant in this patient population (CCI CCI – CCI%). Statistically, the hypothesis that will be tested is H_0: p CCI versus H_1: $p >$ CCI, where p is the proportion of patients who live 6 or more months without disease progression. CCI CCI CCI CCI. If CCI or less are progression free at 6 months RXC004 would be determined not worthy of further investigation with this patient population. The type I and II error rates associated with this testing are 0.06 and 0.10, respectively. The PFS at 6 months estimates 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 patients are expected to be enrolled in order for CCI patients to be evaluable.

Module 2

If the true PFS at 6 month rate with RXC004 were CCI% or less, there is limited interest in developing RXC004 further in this population CCI%). This level is estimated from the ABC-06 trial with mFOLFOX where the median PFS was CCI and DCR was CCI% (Lamarca et al 2019). A 6 month PFS rate of CCI% would be considered to be a clinically significant improvement CCI%). Statistically, the hypothesis that will be tested is H_0: $p <$ CCI versus H_1: $p >$ CCI, where p is the is the proportion of patients who live 6 or more months without disease progression. CCI CCI

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CCI . If CCI or less are progression free at 6 months RXC004 would be determined not worthy of further investigation with this patient population. The type I and II error rates associated with this testing are 0.06 and 0.20, respectively. The PFS at 6 months rate 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 patients are expected to be enrolled in order for CCI patients to be evaluable.

Module 3

In the KEYNOTE-158 and KEYNOTE-028 studies, a combined response rate of approximately CCI% has been observed (Piha-Paul et al 2020), thus an improvement to CCI% would be clinically significant and is used as the CCI in setting the go/no-go hurdles in terms of an efficacy rate that would not want to be missed. CCI

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4.16 Changes in the Conduct of the Study or Planned Analysis

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.

5 REFERENCES

Guideline, ICH Harmonised Tripartite. "Structure and content of clinical study reports E3." Recommended for Adoption at Step 4 (2020).

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., ... & Rubinstein, L. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer, 45(2), 228-247.

6. APPENDICES

Anti-Tumour Activity assessment

The anti-tumour activity of RXC004 will be assessed by Investigator at site by utilizing images from CT or 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).

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.

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 5 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).

5.1.1 Target Lesions (TL) 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 of the individual lesions is missing, the sum of longest diameters is also missing, nevertheless the available sum meets criteria for PD.

5.1.2 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.

5.1.3 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.

5.1.4 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.

Approval Signatures

Document Name: Statistical Analysis Plan 15 Feb 2024 RXC004/0003

Document Number: VV-TMF-6365231

Parexel Version Number:

System Version Number: 1 .0

Document Approvals	
Reason for signing: Approved	Name: PPD Role: PPD Date of signature: PPD
Reason for signing: Approved	Name: PPD Role: PPD Date of signature: PPD
Reason for signing: Approved	Name: PPD Role: PPD Date of signature: PPD
Reason for signing: Approved	Name: PPD Role: PPD Date of signature: PPD