Redx Pharma plc
Protocol #: RXC004/0001

A Modular multi-Arm, Phase 1, Adaptive Design Study to Evaluate the Safety and Tolerability of RXC004, Alone and in Combination with Anti-cancer Treatments, in Patients with Advanced Malignancies

Statistical Analysis Plan

Version 3.0; Amendment 2
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Date	Reason for update	Modifications
	Original version 1.0	NA
07/20/2022	Amendment 1 version 2.0	1. Section VII; Prior Therapies: Summary tables for Best overall response of the immune checkpoint inhibitor regimens added. 2. Section VII; Cancer history and classification: Summary of RNF43 and RSPO status and Wnt Ligand Dependency added. 3. Section VIII; PFS will not be summarized using KM method with cohorts of n=3. 4. Separate plot for diameter of TLs by dose level and wnt ligand dependency added. 5. Section IX, Cumulative dose of RXC004 removed. 6. Cumulative dose and any dose reduction summary table for Nivolumab removed. 7. Section IX, Subsection B-Adverse Events: Separate listing of Serious AE, TEAEs leading to discontinuation of RXC004 and Nivolumab removed. 8. Summary table of any Grade 3 or higher TEAE , related TEAEs for RXC004 and Nivolumab added. 9. Summary table related to RXC004 and Nivolumab added. 10. Summary table of TEAE leading to Nivolumab reduction removed. 11. Summary table related to TEAE by PT added. 12. Section IX, subsection C: Overlaying Line plot for lab data for all subjects added 13. Section IX, subsection I: ECOG shift table by visit is removed. 14. Section IX, subsection J: Post anti-cancer therapy changed to Post-Treatment Anti-Cancer Therapy. 15. Section IX, subsection K: Summary table of B-CTX added.
03/09/2023	Amendment 2 version 3.0	1. Section II, subsection A: Protocol version and date were updated. 2. Section II, subsection C: One of the endpoints was removed as per the new protocol v7.0. 3. Section III, subsection C: Dysgeusia Questionnaire endpoint was added for Module 3. 4. Section IV, subsection A: Actual dose for Module 2 updated. Details regarding Module 3 study design overview added 5. Section IV, subsection B: Study population for Module 3 added 6. Section IV, subsection C: Sample size for Module 3 added 7. Section IV, subsection E: Schedule of Assessments for Module 3 added 8. Section VI, subsection J, point #5: Evaluable for Safety Population for Module 3 added. 9. Section VIII, subsection B: Duration of Response and Time to

		Response analysis excluded for Module 3. 10. Section IX, subsection A: Number of Completed Cycles' calculation for Module 3 added.

TABLE of CONTENTS

List of Abbreviations

Abbreviation or Specialist Term	Definition
AE	Adverse Event
BMD	Bone Mineral Density
BMI	Body Mass Index
CM	Concomitant Medication
CR	Complete Response
ctDNA	Circulating tumor deoxyribonucleic acid
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICF	Informed Consent Form
KM	Kaplan-Meier
MBAD	Minimum Biologically Active Dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Objective Response Rate
PD	Progressive Disease
PDc	Pharmacodynamic
PFS	Progression-free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
QD	Once a day
QTcF	QT with Fridericia's correction
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TL	Target Lesion
WHO	World Health Organization

I. Introduction

The Statistical Analysis Plan (SAP) is based on Protocol RXC004/0001 Version 7.0 dated September 16th, 2022.

This SAP will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein. The plan may be modified until the study clinical database is locked. Modules will be reported separately, so changes to the SAP specific for module 2 and module 3 have been made after the database is locked in module 1. Any deviations from the analysis plan, including any after the database lock, will be documented as such in the study report.

This SAP will govern the analysis of efficacy and safety data from this study as well as descriptive summaries of the pharmacokinetic (PK) and key pharmacodynamic (PDc) data to be included in the CSR.

II. Protocol Objectives

A. Primary Objectives

The protocol lists the following primary objectives which applies to all Modules of the study:

- To assess the safety and tolerability of RXC004 when given to patients with advanced malignances alone or in combination with anti-cancer treatments, and to define the doses and schedules for further clinical evaluation.

B. Secondary Objectives

The protocol lists the following secondary objectives which apply to all Modules of the study:

- To characterize the PK profile of RXC004, following a single dose and at steady state after multiple dosing, when given orally alone or in combination with anti-cancer treatments.
- To obtain a preliminary assessment of RXC004 activity by evaluation of pharmacodynamic (PDc) biomarker changes which may include, but are not limited to, Wnt pathway inhibition, gene expression signatures, and ctDNA levels.
- To obtain a preliminary assessment of the anti-tumor activity of RXC004 as a single agent or in combination with anti-cancer treatments (to include assessment of objective response rate [ORR], disease control rate [DCR], duration of response [DoR], and progression-free survival [PFS])

C. Exploratory Objectives

The protocol lists the following exploratory objectives which apply to all Modules of

the study:

- To obtain a preliminary assessment of RXC004 activity by evaluation of PD biomarkers from blood skin, and tumor, which may include, but are not limited to normal and tumor cell signaling pathway targets and modulation of gene expression, and measures of tumor infiltrating lymphocyte population.
- To explore the relationship between PK and efficacy, safety, and blood borne and tissue biomarkers.
- To collect and store pre-dose plasma and serum sample and/or analyze surplus blood or tissue including patient specific archival tumor tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease and/or response to RXC004 (where response is defined broadly to include efficacy, tolerability or safety). This may include the analysis of tumor specific and circulating biomarkers, such as tumor DNA, mRNA, proteins, or metabolites. In the event that additional tumor molecular profiling is required to understand further any response to RXC004, Redx may request a sample of the most recent tumor biopsy for additional research.
- To investigate predictive markers and acquired resistance to RXC004 that may be observed in tumor from patients treated with RXC004.
- To investigate the per-patient concordance between potential patient selection biomarker (and/or other molecular aberrations) and PDc biomarkers as determined either by Redx or local test methods, in comparison to potential patient selection biomarkers and PDc biomarkers levels obtained by central laboratory tests.
- Characterization in paired tumor biopsies samples of the effect of RXC004 on changes in the tumor microenvironment including but not limited to effects on immune cell subpopulations

III. Study Endpoints

Pharmacokinetics parameter derivation will be handled by PharmaKinetic Ltd. and is not described in this analysis plan.

A. Efficacy Endpoints

- The endpoints for assessment of efficacy include ORR, DoR, DCR, PFS based on the response evaluation criteria in solid tumors (RECIST) Version 1.1

B. Safety Endpoints

- Incidence and severity of AEs and SAEs
- Incidence and severity of dose limiting toxicity (DLT)
- Observed values and change from baseline in clinical laboratory test results which include serum chemistry, hematology, urinalysis, thyroid

function monitoring, lipid panel, liver function tests (LFT) monitoring, bone monitoring (β-CTX).
- Observed values in bone mineral density (BMD) data by using DXA scan.
- Observed values and change from baseline in vital signs
- Observed values and change from baseline in electrocardiogram (ECG) parameters
- Frequency counts and percentages of physical examination findings

C. Dysgeusia questionnaire endpoints*
- Grades for each question – main questions and how taste is altered questions

* Dysgeusia questionnaire data reporting is outside the scope of the SAP.

IV. Study Design

A. Design Overview

The study is a modular Phase 1, dose escalation, open-label study to assess the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumor activity of RXC004 in monotherapy and in combination in patients with advanced malignancies.

The study has three modules: the RXC004 monotherapy module (Module 1),the RXC004 and Nivolumab combination module (Module 2) and the RXC004 monotherapy scheduling module in selected Wnt pathway activated patients (Module 3).

Based on emerging preclinical data and, safety and tolerability information from the initial modules, a Module 4 may be added with a protocol amendment. Thus, this SAP covers modules 1, 2 and 3. Any changes needed for future modules will be covered by an SAP amendment.

For Module 1 – RXC004 Monotherapy:

Module 1 opened in 2018 with a RXC004 dose of 10mg once daily, but the dose was not tolerated in the first patient who developed grade 3 diarrhea, colitis and asymptomatic bone fragility fractures in a thoracic vertebra and clavicle, which are on-target toxicities of Wnt pathway inhibitors. The $T_{1/2}$ in humans was found to be longer than predicted from preclinical models, due to an extended terminal elimination phase resulting in a high Cmin level. Recruitment was halted to allow for the manufacture of lower doses of compound and to amend the protocol with a revised dose schedule and additional safety measures. The Module 1 dose escalation was restarted on 18th March 2019 with 0.5mg and was to commence with an accelerated dose escalation schedule and enroll three patients into a cohort with follow up for adverse events and DLT according to the dose levels in table 1. For the purposes of reporting the 10mg patient will be included in all safety tables and will appear as the top dose studied in the tables.

Dose escalation was to continue in a 3+3 design until the minimally biological active dose (MBAD) has been found to be tolerated. Subsequent dose escalation was to continue in a 3+3 design until maximum tolerated dose/maximum feasible dose (MTD/MFD) has been reached.

Table below shows an indicative dose escalation scheme for Module 1.

Table 1. Indicative Dose Escalation Scheme for Module 1

Dose levels	Planned Dose	Actual Dose
1	0.5 mg QD	0.5 mg QD
2	1.0 mg QD	1.0 mg QD
3	1.5 mg QD	1.5 mg QD
4	2.0 mg QD	2.0 mg QD
5	2.5 mg QD	3.0 mg QD
6	3.0 mg QD	

For Module 2 – RXC004 and Nivolumab Combination:

The reason for conducting Module 2 is to provide the first cancer patient safety and tolerability data with RXC004 in combination with Nivolumab.

Module 2 will commence by enrolling patients with advance solid tumors into a single ascending dose/multiple ascending dose (SAD/MAD) monotherapy dose escalation arm. Eligible patients will be enrolled in dose-escalation cohorts treated with RXC004 given as an oral capsule dose in combination with a PD1 infusion. The dose of Nivolumab will be a fixed dose of 480 mg every 4 weeks and will remain at this dose level throughout the study. The dose of RXC004 will be escalated. The RXC004 starting dose for combination with Nivolumab will be at a minimum of 2 dose levels below the MTD of the monotherapy regimen. The RXC004 dose will be dose-escalated to the MTD in combination in as few dose-cohorts as possible.

Table below shows an indicative dose escalation scheme for Module 2. All dose levels beyond cohort 1 may change in light of emerging safety, tolerability, and pharmacokinetic data, and also evolving relevant pre-clinical data.

Table 2. Indicative Dose Escalation Scheme for Module 2

Dose levels	Planned RXC004 Dose (Starting Cycle 0) *	Planned Nivolumab Dose/Regimen (Starting Cycle 1)	Actual RXC004 Dose (Starting Cycle 0) *	Actual Nivolumab Dose/Regimen (Starting Cycle 1)
1	1 mg QD	480mg q4w	1 mg QD	480mg q4w
2	1.5 mg QD	480mg q4w	1.5 mg QD	480mg q4w
3	2 mg QD	480mg q4w	N/A	N/A

* The first cohort will start with a dose of RXC004 at a minimum 2 dose levels below the MTD of the monotherapy regimen.

For Module 3 – RXC004 Monotherapy Scheduling:

Module 3 will investigate the PK, Wnt pathway inhibition, incidence/severity of Wnt pathway related adverse events and anti-tumor activity of RXC004 when given at 2 different intermittent dosing schedules, in a selected group of patients with Wnt ligand dependent advanced solid tumors.

Following the completion of Module 1, the 2mg QD dose was selected as the recommended starting dose for Phase 2 studies, with options of interruptions and dose reductions to manage potential toxicities. The most frequently occurring treatment related AEs in module 1 (all doses) were fatigue (52%), nausea (44%), decreased appetite (40%), dysgeusia (40%) and vomiting (24%). The median RXC004 exposure in Module 1 was approximately 7 weeks so these adverse events were generally observed during the first two treatment cycles. Of the observed adverse events, only dysgeusia, a known on-target toxicity of Wnt pathway inhibitors, was observed to be dose-related and 4 out of 6 patients in the 2mg cohort reported dysgeusia within the first 2 treatment cycles.

Module 3 will explore whether intermittent dosing schedules have the potential to deliver clinical anti-tumor activity in selected patients with Wnt ligand dependent tumors and whether intermittent dosing, giving short treatment breaks, has the potential to reduce incidence of treatment related toxicities such as dysgeusia. If so, an intermittent dosing schedule could be a future alternative to dose reduction in the management of treatment related adverse events.

Table below shows an Intermittent Dose Schedule for Module 3.

Table 3. Intermittent Dose Schedule for Module 3

Planned Dose	Planned Dose Schedule	Actual Dose	Actual Dose Schedule
2.0 mg QD	2 weeks on/1 week off	2.0 mg QD	2 weeks on/1 week off

B. Study Population

The patient population for this study will include men and women, 18 years or older at the time of screening, with histological or cytological confirmation of advanced malignancy not considered to be appropriate for further conventional treatment.

Additionally, for Module 3, patients with Wnt ligand-dependent solid tumors, defined as Biliary tract cancers, Thymus cancers (thymic and thymoma WHO classification) or any solid tumor with documented aberration in RNF43 and/or RSPO, will be included.

See Protocol Section 2 for a complete list of inclusion/exclusion criteria.

C. Sample Size

The sample size for Module 1 is not based on a formal sample size calculation, as no formal statistical hypothesis is being tested. The estimated maximum number of patients (n=30) has been based on the expected number of cohorts and the desire to obtain adequate tolerability, safety, pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the IMP and procedures. The total number of patients required will depend upon the toxicities encountered and the number of dose cohorts required.

For Module 2, there will approximately 18 patients.

Module 3 will recruit 6 evaluable patients per Arm.

D. Treatment Randomization

This is an open-label non comparative study and as such randomization is not required.

E. Assessment Schedule

See Protocol Appendices 1, 2 and 9 for the study schedule of assessments.

V. Interventions

A. Clinical Trial Material

The RXC004 capsules are provided in 0.5 and 1.0mg strength for oral administration.

Nivolumab will be supplied as 240mg/24mL vial solutions for infusion after dilution. 2 vials will be used per administration (480mg).

B. Study Procedures

Details of study procedures are described in Section 7 of the protocol.

VI. General Analytical Considerations

A. Data Sources and General Rules

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of IQVIA. Data will be captured on eCRFs. Single data entry with source data verification (SDV) will be performed for electronic data capture (EDC). PK and selected PDc data will be transferred to IQVIA. Other PDc, Biopsy, and Biomarker data will be collected and reported from a vendor database for this study.

All statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analysis will be performed using SAS® Version 9.4 with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and programmers.

Tables, listings, and figures will be presented separately for each module of the study. Tables will have separate columns for each dose level and overall, unless otherwise specified. Some summaries and analyses will only be performed at the maximum tolerated dose level (referred as RP2D in below section VIII B)

B. Definition of Baseline

A baseline assessment will be defined as the last assessment performed prior to the first dose of study treatment (RXC004 or Nivolumab if relevant, whichever is earlier). 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.

Change from baseline is calculated as post-baseline value – baseline value. Percent change from baseline is calculated as (post-baseline value – baseline value) / baseline value * 100.

C. Missing Data

Missing safety and efficacy data will not be imputed unless otherwise stated in the sections below.

D. Nominal Timepoints

Except response rate and data presented on continuous timescale, all by-visit summaries and analyses will be performed on nominal visits (i.e., actual visit as specified on the eCRF).

E. Definition of study day

There will be no study day 0. Day 1 is defined as the date of first study treatment. The study day for assessments occurring on or after Day 1 will be calculated as:

- Study day = Date of the assessment/event – Day 1 + 1.

The study day for assessments occurring prior to Day 1 will be negative and calculated as:

- Study day = Date of the assessment/event – Day 1.

The study day will be displayed in all relevant data listings.

F. Multiple Study Centers

No adjustment for study center is planned.

G. Interim Analyses or Timing of Analyses

No formal interim analyses are planned for this study. However, a review of safety data and available PK and PD data will be performed after completion of each dose escalation cohort.

H. Test Sizes

Not applicable as formal statistical hypothesis testing will not be performed. 95% confidence intervals will be provided where specified.

I. Multiple Comparisons

Not applicable.

J. Analysis Populations

Analysis populations will be defined as following:

1. Safety Population

The Safety Population will consist of all patients who enrolled and received at least one dose of any study treatment. The safety population will be used for the safety analyses.

2. Efficacy Evaluable Population

The Efficacy Evaluable Population will include patients who receive a radiographic assessment at baseline, received at least one dose of any study treatment, and at least one post-dose radiographic tumor assessment, or progressed or died ahead of the first scan. The efficacy evaluable population will be used for the efficacy analyses.

3. Pharmacokinetic (PK) Evaluable Population

The PK Evaluable Population will consist of those patients deemed by the sponsor pharmacokineticist to have sufficient PK concentration data to be meaningfully included in the PK analysis summaries.

4. Dose Limiting Toxicity (DLT) Evaluable Population (Module 1 and 2)

For Module 1 and 2, DLT evaluable population is defined as a patient that has received study treatment and either:

- Has completed minimum safety evaluation requirements and has received 100% of the specified RXC004 dose in Cycle 0 and at least 66% of the intended dose of RXC004 during Cycle 1 (Patients in Module 2 must also receive 100% of the nivolumab infusion on Cycle 1 Day 1).
- Has experienced a DLT during Cycle 0 and/ or Cycle 1

5. Evaluable for Safety Population(Module 3)

For Module 3, the evaluable population is defined as a patient that has received study treatment and either:

- Has completed minimum safety evaluation requirements and has received 100% of the specified RXC004 dose in Cycle 0 and at least 80% of the intended dose of RXC004 during Cycle 1 and 2.
- Has permanently discontinued study treatment due to a RXC004-related adverse event

K. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in the following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the eCRF or derived for each patient. They will be ordered by module, dose cohort, site, patient number, and date/time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Summary tables will display summary statistics calculated for each module and dose cohort, as well as overall within each module, unless described otherwise in following sections.

Unless stated otherwise in relevant sections to follow, continuous data will be summarized descriptively with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized using frequency counts and percentages.

VII. Patient Accountability

A. Patient Characteristics

Demographic and baseline characteristics, cancer history and classification, prior therapy will be summarized by dose cohort for each module separately in the Safety Population as appropriate.

Demography and Baseline Characteristics: Data collected about the following patient characteristics at the screening visit will be summarized:

- Age. Age will be calculated as the number of years elapsed between the birth date and the informed consent date.
- Sex and childbearing potential (yes/no)
- Ethnicity
- Race
- Height
- Weight
- Body Mass Index (BMI)

Cancer History and Classification: A summary of the following elements will be provided:

- Duration of Cancer (years). If the full initial diagnosis date is known, duration of cancer is calculated as (date of informed consent minus date of initial diagnosis) / 365.25. For partial initial diagnosis dates, if only month and year is available, the duration will be calculated as (number of months difference between the initial diagnosis year/month and inform consent year/month) / 12. If only year is available for initial diagnosis date, then the initial diagnosis month will be imputed to June that year and the duration will be calculated following the same calculation described above. Stage at Initial Diagnosis
- Primary Location
- Cancer Classification
- Histologic Grade
- RNF43 and RSPO status
- Wnt Ligand Dependency: Wnt Ligand Dependent, Wnt Ligand Independent, Unknown
- TNM Staging at Time of Study Entry
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

Prior Therapies: Summary tables of the following elements will also be provided:

- Prior Anti-Cancer Therapy
    - Number of lines of prior anti-cancer therapies. Combination therapies will be counted as 1 line of therapy.
    - Best overall response to the last anti-cancer regimen prior to the study entry (i.e., date of informed consent).
    - Best overall response among all reported prior anti-cancer regimens.

- Best overall response of the immune checkpoint inhibitor regimens.
- All prior regimens will be coded using the WHO Drug (WHO-DD) version September 2021, B3 Format. The numbers and percentages of patients with prior anti-cancer therapy will be summarized by WHO- DD Anatomical-Therapeutic-Chemical (ATC) classification and preferred term

- Prior Radiotherapy

All data described above will also be provided in the listings.

B. Medical History

Medical histories will be coded using the MedDRA version 24.1 and summarized by System Organ Class (SOC) and Preferred Term (PT) by dose cohort for each module separately.

A data listing will also be provided.

C. Disposition

Disposition will be summarized as the number and percentage of patients enrolled, dosed, discontinued from study treatment along with the reason for discontinuation and discontinued from the study along with the reasons for discontinuation by dose cohort and overall, for each module separately. The number of subjects in each analysis population will be summarized separately.

Enrollment and disposition will be listed in a data listing. Screen failures will also be listed.

D. Protocol Deviations

A summary of number and percentage of patients with any protocol deviation by dose cohort and module based on the Safety Population will be present.

Protocol deviation would be classified into major and minor. protocol deviation will be summarized by major/minor category. In addition, COVID-19 related protocol deviations will be summarized.

VIII. Efficacy Analyses

Efficacy analyses will be based on the Efficacy Evaluation Population.

A. Efficacy Endpoints

The preliminary assessment of efficacy will be assessed via tumor responses and lesion parameters based on the RECIST version 1.1. guidelines. The efficacy analyses of responses including best overall response (BOR), objective response rate (ORR),

duration of response (DoR), disease control rate (DCR) and progression free survival (PFS). The lesion parameters include change and percent change from baseline in the sum of the diameters of target lesions (TLs), presence/absence of non-target lesions and/or new lesions.

All efficacy endpoints will be summarized and analyzed by dose cohorts for Module 1, Module 2 and Module 3 separately unless otherwise specified below.

1. Best Overall Response (BOR)

Categorization of objective tumor response based on RECIST 1.1. guidelines for target lesions include CR (complete response), PR (partial response), SD (stable disease), PD (progression of disease), and NE (not evaluable).

Best overall response is determined based on the RECIST overall responses as assessed by the investigator from the start of first study treatment (RXC004 or Nivolumab if relevant, whichever is earlier) until the end of last study treatment, including any required RECIST scans/assessments for confirmation post the last study treatment.

CR and PR can only be considered as the best overall response if the initial CR or PR is confirmed by a scan that shows the same response or better at least 4 weeks after the initial response. If the repeat scan following the initial response is NE, but the next evaluable response confirms the initial CR/PR response, the BOR of CR/PR will be claimed. For example, a patient with time point responses assessed as PR-NE-PR will be considered as a confirmed PR.

SD does not require confirmation. If SD is the best response ever seen and it meets the minimum criteria for SD duration (at least 35 days from date of first study treatment), SD will be claimed to be the best response overall response.

Below table illustrates the determination of the best overall response when CR or PR confirmation is required.

Table 3. Best Overall Response When Confirmation of CR and PR Required

Overall response Initial response	Overall response Subsequent response	Best overall response
CR	CR	CR
CR	PR	PR
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 provided minimum criteria for SD duration met, otherwise PD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
SD	SD	SD provided minimum criteria for SD duration met, otherwise NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise PD
SD	NE/Missing	SD provided minimum criteria for SD duration met, otherwise NE
PD	Not applicable	PD
NE	NE	NE

2. Objective Response Rate (ORR)

Objective response rate is defined as proportion of patients with a BOR of CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

3. Disease Control Rate (DCR)

Disease control rate is defined as the proportion of all patients dosed that have a visit response of at least SD, PR, or CR at the second schedule scan post baseline, scheduled at week 12 for module 1 and module 3 or week 16 for module 2. Therefore, earlier visit responses of CR, PR that become PD at the second post baseline scan or NE responses at the second post baseline scan do not constitute disease control. A time window of 1 week around the visit will be applied and any visits occurring within 1 week of the scheduled time will be acceptable for inclusion in the assessment; however, if an earlier visit is defined as PD, then the visit response at the second post baseline scan would also be defined as PD. If the second post baseline scan is missing or NE, but the next evaluable response is SD or better, then the patient will be defined as having non-progressive disease at the second post baseline scan visit. Disease control rate will also be assessed separately for the first 3 scheduled post baseline scans (i.e., 18 weeks for module 1 and 3 and 24 weeks for module 2. A separate line in the ORR table will be presented to show the DCR for the

first 2 scan visits and DCR for the first 3 scan visits.

4. Duration of response (DoR)

Duration of response is defined as the time from the date of first documented overall response of confirmed CR or PR until date of first documented progression or death (from any cause), whichever occurs first. The first date at which a CR or PR response was noted will be used to calculate DOR, not the

date of the confirmatory tumor assessment. Unconfirmed response will not be included.

Patients who do not experience disease progression or death following a response at the time of analysis will be censored at the date of last tumor assessment by RECIST 1.1 criteria.

Duration of response will only be evaluated for patients who have a best overall response of CR or PR.

5. Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time from the date of first study treatment (first dose of RXC004 or Nivolumab if relevant, whichever is first) until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy prior to progression/death. Date of progression will be determined based on the date of first radiological assessment indicating progression (i.e., first scan date when an overall response is determined to be progressive disease as assessed by the investigator per RECIST overall response CRF page).

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of scan/assessment from their last evaluable RECIST assessments. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST scan/assessment prior to the missed visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at 1 day unless they die within 2 scan visits of baseline.

Lesion parameters will be assessed at each RECIST assessment, including target lesion diameter (for lymph nodes, the shortest diameter will be collected; for soft tissue lesions, the longest diameter will be collected), presence/absence of non-target lesions; and presence/absence of new lesions.

The sum of the diameter of target lesions will be calculated at each RECIST assessment. Change and percent change from baseline in the sum of diameter of TLs will also be calculated.

The best percentage change in tumor size while on treatment will be the patient's value representing the largest decrease (or smallest increase for those patients whose target lesions do not show a decrease) from baseline in the sum of diameter of TLs.

B. Efficacy Endpoint Analyses

ORR and DCR will be summarized for all dose levels. The two-sided 95% confidence interval (CI) using the Clopper-Pearson method will only be provided at RP2D and overall.

PFS, and DoR will be summarized using the Kaplan-Meier (KM) method at by treatment group and overall. Estimates of median and PFS at 6 and 12 months, with the corresponding 95% CI will be reported for RP2D and overall. Swim lane plot for all time to event analysis by dose level and by wnt ligand dependency (DOR, PFS and duration of treatment).

Time to response, defined as (date of first documented response of CR or PR for patients who have a confirmed CR or PR – date of first treatment + 1) / 7, will be summarized descriptively among patients who reported a response.

Percent change from baseline in the sum of diameters of TLs will be summarized descriptively. Percent change from baseline in the sum of diameters of TLs for individual patient will be present in the spider plots – separate plots will be done by dose level and by Wnt ligand dependency. The best percent change in tumor size while on treatment will be presented in two waterfall plots. In one plot the bars will be color coded by dose level and in a separate plot by Wnt ligand dependency.

ORR and percent change in the sum of TL diameters will only be evaluated among patients with measurable disease (i.e., with target lesion identified) at baseline. All efficacy data as collected on the eCRF along with the derived parameters will be presented in data listings.

Given the small sample size in module 3, Duration of Response (DoR) and Time to Response will not be summarized for module 3 patients.

IX. Safety Analyses

Safety analyses will be based on the Safety Population.

A. Exposure

Exposure to RXC004 and Nivolumab will be summarized by dose cohorts and overall, for each module separately. All exposure parameters as well as all exposure data collected on the eCRF will be present in data listings.

The following exposure parameters of RXC004 will be summarized from the

start of Cycle 0.

- Total duration of exposure (weeks): calculated as (last RXC004 dosing date – first RXC004 dosing date + 1) / 7
- Total number of doses received: defined as number of doses received as collected on the RXC004 dose administration eCRF page from the first RXC004 dosing date to the last RXC004 dosing date.
- Any dose modifications: patients who have at least 1 RXC004 dose change (including dose reduction, missed dose or dose permanently withdrawn) along with the reason for dose modification will be summarized using frequency counts and percentages.
- Any dose reductions: patients with any dose reductions will be summarized using frequency counts and percentages by the following categories: any dose reductions, 1 dose reduction, 2 dose reductions.

The following exposure parameters of RXC004 will be summarized based on continuous dosing period (i.e., start from Cycle 1 Day 1). Cycle 0 dosing is excluded:

- Total duration of exposure (weeks) on continuous dosing: calculated as (last RXC004 dosing date – first RXC004 dosing date of C1D1 + 1) / 7
- Number of cycles for RXC004 on continuous dosing excluding Cycle 0: will be determined based on the last nominal visit as collected on CRF
- Number of completed cycles: a cycle will be considered complete if they have 14 days of therapy within a 3-week period from C1D1. The total number of completed cycles will be calculated as the total number of days the dose was received divided by 14 (Module 3 only).
- Cumulative actual dose received (mg): defined as total amount of actual dose (mg) received as collected on the RXC004 dose administration eCRF page from the first RXC004 dosing date to the last RXC004 dosing date.
- Cumulative planned dose (mg): defined as total amount of planned dose (mg) as recorded on the RXC004 dose administration eCRF page from the first RXC004 dosing date to the last RXC004 dosing date.
- Actual dose intensity (mg/week): defined as cumulative actual dose (mg) divided by total duration of exposure (weeks)
- Planned dose intensity (mg/week): defined as cumulative planned dose (mg) divided by total duration of exposure (weeks). If a patient had a reduced dose per investigator's assessment, then reduced dose will be considered as planned dose for the calculation of RDI.
- Relative dose intensity (%): calculated as (actual dose intensity / planned dose intensity) * 100%.
- Relative dose intensity category: the calculated % relative dose intensity above will be summarized by the following categories using frequency counts and percentages: <60%; 60% ≤ and < 75%; 75% ≤ and < 90%; 90%≤ and ≤ 100%; > 100%.

The number of capsules dispensed, returned and taken at each visit as collected on the RXC004 drug accountability eCRF page will be presented in data listings.

Duration of the RXC004, will be summarized as continuous variables.

For patients in Module 2, the following exposure parameters of Nivolumab will also be summarized:

- Total number of doses received: defined as number of doses received as collected on the Nivolumab dose administration eCRF page from the first Nivolumab dosing date to the last Nivolumab dosing date.
- Any cycle delay: patients who have any cycle delay, 1 cycle delay, 2 cycle delays, >= 3 cycle delays will be summarized using frequency counts and percentages.
- Any infusion interruption: patients who have any infusion interruption along with the reason will be summarized using frequency counts and percentages.

Number of Nivolumab doses will be summarized as continuous variables.

B. Adverse Events

Adverse events will be coded using MedDRA version 24.1. AEs are graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

A treatment-emergent AE (TEAE) is defined as AEs that first occurred or worsened in severity after the first administration of the study treatment (RXC004 or Nivolumab) and within 30 days of last dose of RXC004 in the case of Module 1 and Module 3 and within 90 days of last dose of Nivolumab for Module 2.

If relationship to RXC004 or Nivolumab is missing, the event will be conservatively treated as related to the corresponding study treatment. Missing CTCAE grade will be summarized as separate category.

All AEs will be listed by module, dose cohort and patient, detailing the verbatim term given by the investigator, the preferred term (PT), system organ class (SOC), onset date, stop date, CTCAE grade, relationship to RXC004, relationship to Nivolumab (Module 2 only), action taken with RXC004, action taken with Nivolumab (Module 2 only), other action taken, dose limiting toxicity (Y/N), caused by disease progression (Y/N) and seriousness. Dose limiting toxicity.

An overall AE summary will be present by the number and percent of patients for each module separately with the following:

- All AEs
- All TEAEs
- Dose limiting toxicity (DLTs) (Module 1 and 2 only)
- RXC004-related TEAEs

- Any TEAE of CTCAE of grade 3 or higher
- Any TEAE of CTCAE of grade 3 or higher related to RXC004
- Nivolumab-related TEAEs (Module 2 only)
- Any TEAE of CTCAE of grade 3 or higher related to Nivolumab (Module 2 only)
- Serious AEs
- RXC004-related SAEs
- Nivolumab-related SAEs (Module 2 only)
- TEAEs leading to RXC004 withdrawal
- TEAEs leading to Nivolumab withdrawal
- TEAEs leading to RXC004 reduction
- RXC004 related adverse event leading to death
- Nivolumab-related adverse event leading to death (Module 2 only)
- TEAEs leading to RXC004 interruption
- TEAEs leading to Nivolumab interruption
- AEs leading to death

The following AE summaries will be produced by system organ class (alphabetical order) and preferred term (descending order of the overall frequency) for each module separately:

- All TEAEs
- Serious AEs
- Grade 3 or higher TEAEs
- TEAEs leading to RXC004 withdrawal. This subset includes TEAEs with an Action Taken with RXC004 of "Drug Permanently Withdrawn" on the AE form.
- TEAEs leading to RXC004 reduction. This subset includes TEAEs with an Action Taken with RXC004 of "Dose reduced" on the AE form
- TEAEs leading to RXC004 interruption. This subset includes TEAEs with an Action Taken with RXC004 of "Dose interrupted" on the AE form
- TEAEs leading to Nivolumab withdrawal (Module 2 only). This subset includes TEAEs with an Action Taken with Nivolumab of "Drug Permanently Withdrawn" on the AE form.
- TEAEs leading to Nivolumab interruption (Module 2 only). This subset includes TEAEs with an Action Taken with Nivolumab of "Dose interrupted" on the AE form
- TEAEs related to RXC004. This table will include TEAEs with a drug relationship of "Possibly Related" or "Probably Related" to RXC004.
- TEAEs related to Nivolumab (Module 2 only). This table will include TEAEs with a drug relationship of "Related" to Nivolumab.
- SAEs related to RXC004
- SAEs related to Nivolumab (Module 2 only)
- Grade 3 or higher TEAEs related to RXC004
- Grade 3 or higher TEAEs related to Nivolumab (Module 2 only)
- AEs leading to death

- AEs considered as dose-limiting toxicity (DLT) (Module 1 and 2 only)
- TEAEs by maximum CTCAE grade
- TEAE by PT
- Treatment Related TEAE by PT.

At each level of summarization, a patient will be counted once if he/she reported one or more events. The maximum CTCAE grade will be taken for the purposes of the summaries by grade.

In addition, all deaths as collected on the Death eCRF page will be present in a data listing.

C. Clinical Laboratory Results

Laboratory test results (including serum chemistry, hematology, urinalysis, lipid panel, bone monitoring, liver function testing and thyroid panel [Module 2 only]) and abnormal laboratory values will be presented in data listings. CTCAE version 5.0 lab grades will also be presented where applicable. CTCAE grades will be derived based on laboratory results and will not factor in clinical evaluations. 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 version 5.0 results will be classified as low, normal, or high based on laboratory normal ranges.

Overlay line plot of observed values of lab data (including serum chemistry, hematology, urinalysis, lipid panel, bone monitoring, liver function testing and thyroid panel [Module 2 only]) will be presented for all subjects and by study module. Hys law eDISH plot will also be presented.

Shift tables will be used to summarize the changes from baseline in severity of lab CTCAE grades for will be provided for serum chemistry, hematology, and urinalysis parameters by module, dose cohorts and visit, starting from the first post-baseline visit. The shift from baseline to worst low lab grades and to worst high lab grades will be summarized by module and dose cohorts. Clinical evaluations (normal, abnormal not clinically significant, and abnormal, clinically significant) will be summarized using frequency counts and percentages for each visit as applicable. For numeric laboratory test results, summaries of actual values, changes from baseline, and percent change from baseline will also be summarized using continuous descriptive statistics at each visit.

By-patient listing will be provided by visit, including changes from baseline, grade and reference range. All values outside the 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.

Results from pregnancy tests and HIV status will be provided in data listings.

D. Vital Signs

Actual values and change from baseline of vital signs data (weight, temperature, pulse, respiratory rate, systolic blood pressure, and diastolic blood pressure) will be summarized using descriptive statistics at each visit. A listing of the vital signs data will also be provided.

E. Physical Examination

A full physical examination is assessed at screening and prior to Day 1 of each cycle. Abnormal physical examination findings will be presented in data listings.

F. Electrocardiogram (ECG)

Actual values and change from baseline of ECG parameters (PR interval, RR interval, QRS duration, QT interval, QTcB, QTcF) will be summarized descriptively by module, dose cohorts and timepoints. Note that ECGs are collected in triplicate and analyses of numeric results will be based on the average of the triplicate results.

All ECG results along with the overall evaluation [i.e., Normal, Abnormal, Not Clinically Significant, and Abnormal, Clinically Significant]) will be presented in data listings.

QTcF interval absolute values will also be tabulated by the following groups:

- <=450
- >450-<=480 msec
- >480-<=500 msec
- >500 msec

Change from baseline in QTcF interval will be classified as:

- <=30 msec increase from baseline
- >30-<=60 msec increase from baseline
- >60 msec increase from baseline

Frequency and percentage of QTcF categorical analysis will be summarized by module and dose cohorts. 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

G. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date prior to the first dose of any study treatment. Concomitant medications are defined as medications ongoing or with stop dates on or after the first dose of any study treatment. Prior and concomitant medications will be coded using WHO Drug version March 2021, B3 Format.

To distinguish prior vs. concomitant medications, the following rules for stop dates will apply:

- If only year is recorded, and it is before Day 1, it is a prior medication; if year is same or after Day 1, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Day 1, it is a prior medication; if month and year are the same as Day 1, it is assumed to be a concomitant medication; if month and year are after Day 1, it is a concomitant medication.
- If start date is after Day 1, it is a concomitant medication regardless.

Concomitant medications will be summarized by module, dose cohort, WHO-DD ATC classification, and PT.

All prior and concomitant medications will be displayed in data listings as well.

H. Prior and Concomitant Procedures

Prior procedures are defined as procedures with a procedure date that is prior to the first dose of any study treatment. Concomitant procedures are defined as procedures with a procedure date on or after the first dose of any study treatment.

Prior and concomitant procedures will be coded using MedDRA version 24.1. Concomitant procedures will be summarized by SOC and PT by dose cohort for each module separately.

All prior and concomitant procedures will be displayed in data listings as well.

I. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

A shift table of ECOG performance status from baseline to worst on-treatment value will be provided by dose cohort for each module separately.

A listing of ECOG performance status results will also be generated.

J. Post Treatment Anti-Cancer Therapy

Post treatment Anti-Cancer therapy data will be summarized by ATC and PT in the summary table and presented in the data listing.

K. β -CTX

Absolute and change from baseline of β -CTX will be summarized and listed by

dose level and study module. β -CTX results below the lower limit of

quantification will be imputed as 0 in descriptive summaries. Subjects who received denosumab will be summarized and flagged in the listings and if clear distinction between cohorts will be noted as a footnote in the summary table.

L. Other Assessments

DXA scan results, including change from baseline in BMD, concomitant radiotherapy, and concomitant transfusions will be presented in the data listings.

X. Pharmacokinetics Analyses

Plasma concentration data will be listed and summarized descriptively by analyte, module, dose level and nominal time points.

Descriptive statistics will include the number of patients (n), mean, SD, coefficient of variation (CV%), median, minimum, and maximum. Concentration values below the limit of quantification (BLOQ) will be treated as 0 for the computation of descriptive statistics.

The detailed derivation for the pharmacokinetic parameters based on plasma concentration data will be described in a separate analysis plan. All reported PK parameters will be listed and summarized descriptively similar to the concentration data. Geometric mean will also be presented for PK parameters such as AUC, Cmax and other parameters as appropriate and medians for Tmax. Plots of mean PK concentrations will be done with a different line and color for each dose level. Individual subject concentration data will be plotted with separate plots for each dose level.