Cover page

Protocol number: RXC004/0003

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

Version number: 6.0 rev1

Date of the document: 04 January 2023

Clinical Study Protocol	
Study Code	RXC004/0003
Version	6.0 rev1
Date	04 January 2023

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

Legal Registered Address:

Redx Pharma Plc
Block 33
Mereside, Alderley Park
Alderley Edge, Cheshire
SK10 4TG, UK

Regulatory Agency Identifier Number(s)

EudraCT Number: 2020-005804-20

Protocol Number: RXC004/0003

Amendment Number: 05

Study Treatment: RXC004 monotherapy or RXC004 and pembrolizumab combination

Short Title: Phase II Study to Assess RXC004 Efficacy in Advanced Solid Tumours after Progression on SoC Therapy

PORCUPINE2 STUDY

Pancreatic Cancer Module also known in UK as: PRIMUS 007

Biliary Tract Cancer Module also known in UK as: ABC-13

Study also known in Australia as: MoST PORCUPINE2

Merck protocol number: MK-3475-E86

Medical Monitor name and contact information will be provided separately

International co-ordinating investigator

PPD
PPD
PPD
PPD
PPD
Phone: PPD

SIGNATURES

PROTOCOL 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

PROTOCOL NO: RXC004/0003

VERSION NO: 6.0 rev1

PPD

PPD

PPD **Signature** **Date**

PPD

PPD

INVESTIGATOR SIGNATURES

PROTOCOL 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

PROTOCOL NUMBER: RXC004/0003

VERSION NUMBER: 6.0 rev1

This protocol is a confidential communication of Redx Pharma, plc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Redx Pharma, plc.

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

_____

_____

Site Number: _____

VERSION HISTORY

VERSION HISTORY	
Amendment 5 (Version 6.0 rev1)	04 January 2023
Amendment 5 (Version 6.0)	15 December 2022
Amendment 4 (Version 5.0)	19 August 2022
Amendment 3 (Version 4.0)	17 November 2021
Amendment 2 (Version 3.0)	19 June 2021
Amendment 1 (Version 2.0	09 March 2021
Original Protocol	14 December 2020

Amendment 5 (Version 6.0 rev1, 04 January 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Version 6.0 rev1 – 04 January 2023

Version 6.0 - 15 December 2022

Substantial changes:

Revision and addition of text relating to pembrolizumab, including background, risks, eligibility criteria, lifestyle considerations, access to study treatment after the end of the study, discontinuation of study treatment, prohibited and restricted concomitant medications, thyroid function tests, time period for collection of AE and SAE information, follow-up in the event of pregnancy, overdose, Events of Clinical Interest for pembrolizumab.

- **Sections updated: Sections 2.2.4, 2.3.3, 5.1, 5.4, 5.5, 5.6, 6.1.1, 6.2, 6.4, 6.5, 6.6, 7.1, Table 13, 8.3.1, 8.3.9, 8.3.10.1, 8.4, 9.4.3.1, 12.3.1, 12.7, 12.9, and Appendix K.**
- **New Sections added: 12.5.3, 12.7.1, 12.8, 12.10, and Appendix L.**

Non-substantial changes:

Protocol number known to collaborating partner added on page 1 (rev1)

Update to number of colitis events reported in Phase 2 studies:

- **Sections updated: 2.3.1.2 and Appendix K.**

Clarification of data collection for any participant who considers withdrawing from the study:

- **Section updated: Section 7.2.**

Clarification on timing of scans for tumour assessments:

- **Section updated: Section 8.1.1.**

Inclusion of ± 3 days window for the 90-day follow-up visit in Module 3

- **Section updated: Study Assessments (**Table 18**).**

Revision of the text where appropriate to address UK regulatory agency condition (rev1):

- **Sections updates: 5.1, 5.3, 5.4, 5.6.3.1, 5.8**

Details of the protocol amendment history are located in Appendix M.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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 (PORCUPINE2)

Short Title: Phase II Study to Assess the Efficacy of RXC004 in Advanced Solid Tumours that have Progressed following Standard of Care Therapy (PORCUPINE2).

PORCUPINE2 STUDY

Pancreatic Cancer Module also known in UK as: PRIMUS 007

Biliary Tract Cancer Module also known in UK as: ABC-13

Study also known in Australia as: MoST PORCUPINE2

Rationale:

The Wnt-signalling pathway plays an important role in tumourigenesis and has been shown to be hyper-activated in both biliary tract cancers (BTC) and ring finger protein 43 (RNF43) mutated cancers. RXC004 is a small molecule porcupine (PORCN) inhibitor which reduces Wnt signalling and therefore may offer an opportunity to deliver clinical benefit in tumours that have aberrant activation of Wnt signalling.

The PORCUPINE2 study will therefore evaluate the efficacy of RXC004 in advanced solid tumours. The study opened with a RNF43 loss of function (LoF) mutation-positive pancreatic cancer (PANC) module (Module 1) and a molecularly unselected BTC module (Module 2). The BTC Module 2 was initiated with an evaluation of RXC004 2 mg (Cohort 1), continuous dosing. A lower dose cohort to evaluate RXC004 1 mg will also be opened (Cohort 2), dependent on emerging data from the RXC004 2 mg dose cohort, in order to characterise the dose-response relationships for activity and safety and to support the optimal dosage for future clinical development.

Module 3 will evaluate RXC004 1.5 mg in combination with pembrolizumab in patients with BTC.

Further modules (or cohorts within modules) evaluating the efficacy of RXC004 in other advanced solid tumours or with alternative doses/schedules may be added at a later date.

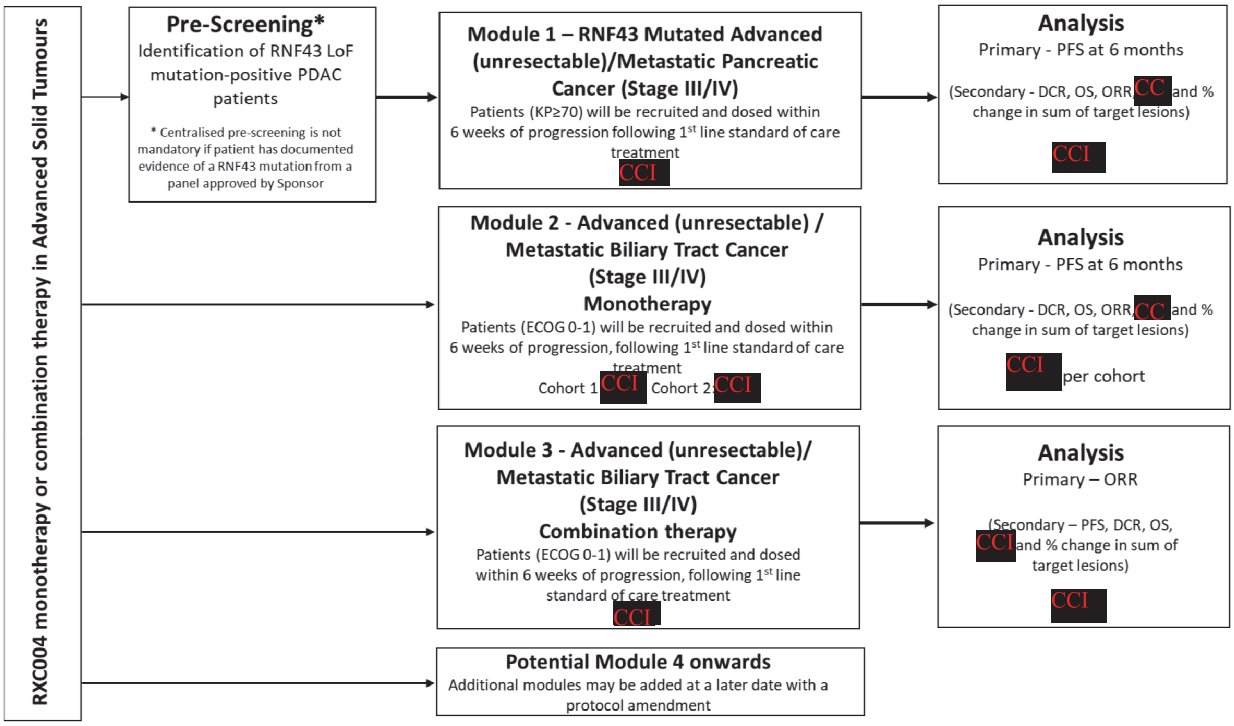
Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the anti-tumour activity of RXC004 as monotherapy and as combination therapy	• 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 as monotherapy and as combination therapy	• Monotherapy (Modules 1 and 2): 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 as monotherapy and as combination therapy	Maximum plasma concentration (C_{max}) after Dose 1, C_{max} at steady state, minimum observed plasma concentration (C_{min}) at steady state as well as other relevant parameters (e.g. t_{max}, $t½$, λz, $AUC_{0-\infty}$, CL/F, and Vz/F).
Safety	
To assess the safety and tolerability profile of RXC004 as monotherapy and as combination therapy	Incidence of AEs SAEs, dose reductions, interruptions and discontinuations, and assessment of dysgeusia
Exploratory	
CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI
CCI CCI CCI	CCI CCI CCI

Objectives	Endpoints
CCI CCI	
CCI CCI CCI CCI	CCI CCI CCI
CCI CCI CCI	CCI CCI CCI CCI
CCI CCI CCI CCI CCI	CCI CCI CCI CCI
CCI CCI	CCI CCI CCI

BOR, best overall response; CCI; CCI; CCI CCI; PFS, progression-free survival; PK, pharmacokinetic(s).

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.

Disclosure Statement: This is an open label study.

Number of Participants:

Approximately CCI patients will be enrolled in total to provide CCI evaluable patients in each Cohort/Module.

Enrolled	Module 1 (PDAC) Estimated CCI patients Module 2 (BTC - Monotherapy) Estimated CCI patients: CCI in each of Cohorts 1 and 2) Module 3 (BTC) Estimated CCI patients
Evaluable patients	Module 1 (PDAC) CCI patients Module 2 (BTC - Monotherapy) CCI patients (CCI in each cohort) Module 3 (BTC - Combination therapy) CCI patients

Note: "Enrolled" means a patient who receives a dose of RXC004. Potential patients who are screened for the purpose of determining eligibility for the study, but are not enrolled are considered 'screen failures'. CCI [redacted]

2 INTRODUCTION

The Wnt signalling pathway plays an important role in tumourigenesis (Zhan et al 2016) and in immune evasion (Goldsberry et al 2019) and is aberrantly activated in many cancers (Loilome et al 2014, Makena et al 2019, Murillo-Garzon and Kypta 2017, Kleeman et al 2020).

PORCN is a membrane-bound protein-serine O-palmitoleoyltransferase which is required for the acetylation, activation and secretion of Wnt ligands. RXC004 is a small-molecule PORCN inhibitor which reduces both canonical and non-canonical Wnt signalling and hence may have clinical benefit in a number of advanced solid tumours.

2.1 Study Rationale

RXC004 is a small molecule PORCN inhibitor which reduces Wnt signalling and therefore may offer an opportunity to deliver clinical benefit in tumours that have aberrantly activated Wnt signalling.

RXC004 may offer an opportunity to deliver clinical benefit by both a direct tumour targeting effect in tumours with aberrantly activated Wnt signalling and an immune-oncology effect, by converting the tumour microenvironment from an immune “cold” to an immune “hot” signature.

This study will evaluate the efficacy of RXC004 in advanced solid tumours for which there is published evidence of aberrantly activated Wnt signalling. The study initially opened with two monotherapy modules:

- Module 1 - RNF43 LoF mutation-positive pancreatic ductal adenocarcinoma (PDAC)
- Module 2 - Biliary tract cancer (BTC)
- Module 3 - Incorporated with protocol amendment 4, will investigate RXC004 in combination with pembrolizumab in BTC.

The rationale for each of these patient populations can be found in the Module specific sections (Section 10 and Section 11 for PDAC and BTC, respectively).

Further modules (or cohorts within modules) evaluating the efficacy of RXC004 in other advanced solid tumours or with alternative doses/schedules may be added at a later date.

2.2 Background

2.2.1 Wnt Signalling in Cancer

The Wnt pathway is initiated by the binding of Wnt glycoproteins to Frizzled (Fz) and low-density lipoprotein receptor-related protein (LRP) 5 or 6 co-receptors, resulting in the

phosphorylation of Dishevelled (DSH) which in turn recruits a destruction complex comprising axin, adenomatous polyposis coli (APC) and glycogen synthase kinase 3β (GSK3β) to the cell membrane. The movement of these proteins inhibits the phosphorylation of β-catenin allowing β-catenin to accumulate near the cell nucleus and induces the transcription of target genes.

The Wnt signalling pathway is aberrantly activated in many cancers (Loilome et al 2014, Makena et al 2019, Murillo-Garzon and Kypta 2017, Kleeman et al 2020) and this can arise through either mutational or non-mutational alterations. Activating mutations have been observed in positive regulators of the Wnt pathway (e.g. β-catenin and TCF transcription factors) and loss of function mutations in negative regulators (e.g. APC, AXIN and RNF43). Non-mutational aberrations include gene fusions (e.g. RSPOs), Wnt receptor copy number gains (e.g. LRP5).

RNF43 is an integral-membrane E3 ubiquitin ligase that promotes degradation of Fz receptors. LoF RNF43 mutations have been described in 5-10% of all pancreatic (Jiang et al 2013, Waddell et al 2015, Bailey et al 2016), 3-13% of all colorectal cancers (Matsumoto et al 2020 and Cerami et al 2012) as well as some gastric and lung cancers (Hao et al 2016). These LoF RNF43 mutations lead to increased Fz receptors at the cell surface and hence hyper-activated Wnt signalling.

There is also strong scientific rationale, from both preclinical and clinical studies, that Wnt pathway activity drives the immune evasion of tumours (Spranger and Gajewski 2018, Wang et al 2018). Porcupine inhibition has the potential to block 2 of the 5 critical mechanisms of tumour cell immune evasion (Wang et al 2018). High β-catenin protein levels (i.e. high Wnt pathway activation) were recently reported to correlate with lack of immune signature across 22 different cancer types (Luke et al 2019). The lack of immune signature has been linked to a lack of response to immune checkpoint inhibitors such as anti-programmed cell death-1 (PD-1). Redx has demonstrated efficacy by an immune system mechanism with RXC004 in combination with an anti-PD1 antibody in a CT26 mouse syngeneic colorectal tumour model. RXC004/anti-PD-1 combination therapy results in a significant decrease in Treg cells and a significant increase in the cytotoxic T-cell to regulatory T-cell (Treg) cell ratio in this model compared to either agent alone. In addition, RXC004 has monotherapy efficacy in the B16 melanoma mouse syngeneic model. This efficacy is dependent on an intact immune system and correlates with RXC004 causing a decrease in myeloid derived suppressor cells (MDSCs) in the tumours of this model.

2.2.2 PORCN Inhibitors

Blocking Wnt signalling with PORCN inhibitors has been shown to suppress the growth of tumours in numerous pre-clinical models (Madan et al 2016, Koo et al 2015, Boulter et al 2015, Noll et al 2016, Jiang et al 2013).

Currently, there are no PORCN inhibitors approved for therapeutic use. A number of companies are investigating porcupine inhibitors in Phase 1/2 clinical trials (e.g. WNT974, ETC-159, XNW7201 and CGX1321). The results from a Phase 1 study of the small molecule PORCN inhibitor WNT974, indicated WNT974 monotherapy had a manageable safety profile and the potential for antitumor activity in a molecularly selected population (Janku et al 2015, Rodon et al 2021). In addition, preliminary data from the dose escalation part of an ongoing Phase 1 study of WNT974 in combination with the anti-PD-1 monoclonal antibody, spartalizumab, in patients with advanced solid tumours have been reported (Janku et al 2020). Of 27 enrolled patients (as of 02 September 2019), 63% had received prior anti-PD-1 therapy. One patient (4%) had a partial response, 11 (41%) had stable disease (SD), 13 (48%) had progressive disease, and response was unknown in 2 patients. The combination of WNT974 + spartalizumab was reported as being well tolerated. Dose-limiting toxicities were reported in 2 patients: Grade 2 spinal compression fracture that occurred in the setting of trauma and Grade 3 arthralgia. The most common treatment-related AE was hypothyroidism (19%). Four patients (15%) had 7 suspected-related Grade 3/4 AEs (arthralgia, atrial fibrillation, diabetes mellitus, diabetic ketoacidosis, hyperglycaemia, hyponatremia, and maculopapular rash).

Phase 1a safety data from an ongoing first-time-in-man clinical study of the small molecule PORCN inhibitor ETC-159, was presented in a poster at the ASCO 2017 annual meeting (Ng et al 2017). Initial analysis showed that ETC-159 had both manageable toxicity and five out of the first twenty patients achieved a best overall response of SD.

2.2.3 RXC004

RXC004 is a potent and selective small molecule inhibitor of PORCN that is required for the post-translational modification of all Wnt ligands. Inhibition of PORCN reduces both Wnt secretion and downstream canonical and non-canonical Wnt signalling. RXC004 has demonstrated in vitro and in vivo efficacy in preclinical models with upstream Wnt pathway aberrations. RXC004 has demonstrated an immune stimulatory effect in combination with an anti-PD-1 antibody in tumours of mouse syngeneic models, which supports testing of the combination of RXC004 with pembrolizumab; see current RXC004 Investigator's Brochure (IB).

RXC004 is being assessed in the Phase 1 RXC004/0001 trial (NCT03447470) as monotherapy and also in combination with the anti-PD-1 monoclonal antibody nivolumab, for safety and tolerability in advanced malignancies. RXC004 monotherapy at doses of 0.5, 1.0, 1.5, 2.0, 3.0, and 10 mg QD have been evaluated to date. RXC004 at doses of 1.0 and 1.5 mg QD has been evaluated in combination with nivolumab.

In addition, RXC004 is being tested as monotherapy in an ongoing Phase 2 study RXC004/0002 in patients with RNF43/RSPO-aberrated metastatic microsatellite stable colorectal cancer following progression on SoC therapy. Combination treatment with RXC004

and nivolumab is also planned in study RXC004/0002.

A detailed description of the chemistry, pharmacology, and pre-clinical efficacy, and safety of RXC004 is provided in the RXC004 IB.

As of 30 July 2021, a total of 25 patients have been dosed with RXC004 monotherapy in the Phase 1 study – at doses between 0.5mg and 10 mg QD. The most frequently occurring TEAEs were fatigue (64%), nausea (56%), decreased appetite (48%), vomiting (40%), dysgeusia (40%), diarrhoea (32%), aspartate aminotransferase increased (28%), anaemia (20%) and constipation (22%). The most frequently occurring TRAEs of any grade were fatigue (52%), nausea (44%), decreased appetite (40%), dysgeusia (40%) and vomiting (24%). Doses up to 2 mg QD were considered safe and tolerable. Events of intestinal inflammation (colitis, enteritis or enterocolitis) were observed in four patients who started treatment with RXC004 at doses of ≥3 mg QD and three of these were dose-limiting toxicities.

A detailed description of the Phase 1 study results is provided in Section 4.4.1.

2.2.4 Pembrolizumab

2.2.4.1 Background

Pembrolizumab is a potent humanised immunoglobulin G4 (IgG4) monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

Refer to the IB/approved labelling for detailed background information on MK-3475 (pembrolizumab).

2.2.4.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes in cancer tissue and favourable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ Tregs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumour-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumour responses in cancers such as melanoma (Dudley et al 2005, Hunder et al 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al 2005, Okazaki et al 2001).

The structure of murine PD-1 has been resolved (Zhang et al 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signalling cascade (Chemnitz et al 2004, Okazaki et al 2001, Riley 2009, Sheppard et al 2004). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signalling proteins (Francisco et al 2010, Parry et al 2005). As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in BTC.

2.2.4.3 Pre-clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumour-specific CD8+ T cells and ultimately leads to tumour rejection, either as a monotherapy or in combination with other treatment modalities (Blank et al 2004, Curran et al 2010, Pilon-Thomas et al 2010, Hirano et al 2005, Spranger et al 2014, Strome et al 2003, Weber 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukaemia, and colorectal carcinoma (Curran et al 2010, Nomi et al 2007, Pilon-Thomas et al 2010, Strome et al 2003, Zhang et al 2004). In such studies, tumour infiltration by CD8+ T cells and increased interferon-γ (IFN-γ), granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumour activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T-cell function in vivo (Curran et al 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumour models (see the IB).

2.2.4.4 Clinical Trials of Pembrolizumab in Patients with Biliary Tract Cancer

Pembrolizumab has demonstrated anti-tumour activity in patients with advanced BTC who had no other options for standard therapy, in 2 clinical studies (KEYNOTE-028 and KEYNOTE-158) (Piha-Paul et al 2020). The primary efficacy endpoint for each study was ORR by RECIST v1.1. The Phase 1b KEYNOTE-028 study enrolled 24 patients; median follow-up was 5.7 months. The ORR was 13.0% (3/23; 95% CI: 2.8%-33.6%); median DOR was not reached (range, 21.5-53.2+ months). Median (95% CI) OS and PFS were 5.7 (3.1-9.8) and 1.8 (1.4-3.1) months. The Phase 2 KEYNOTE-158 study enrolled 104 patients; median follow-up was 7.5 months. In KEYNOTE-158, ORR was 5.8% (6/104; 95% CI, 2.1%-12.1%); median DOR was not reached (range, 6.2-26.6+ months). Median (95% CI) OS and PFS were 7.4 (5.5-9.6) and 2.0 (1.9-2.1) months. The safety profile of pembrolizumab in patients with BTC in these 2 studies was manageable, and no new safety signals were identified. Pembrolizumab is currently being investigated, in combination with standard cisplatin and gemcitabine chemotherapy, as a first-line treatment option for patients with advanced or unresectable BTC in a Phase 3 study, KEYNOTE-966 (NCT04003636).

2.3 Benefit-Risk Assessment

2.3.1 RXC004 Risks

2.3.1.1 Risks Associated with Targeting the Wnt Pathway

The principal on-target adverse events of significant interest known to occur with porcupine inhibition include decreases in bone density (including bone fragility fractures) and loss of taste (dysgeusia). Inhibiting the Wnt pathway may also predispose to inflammation in the gastrointestinal tract because of the role of Wnt in the immune micro-environment.

The safety profile of RXC004 is similar to that reported for two other Porcupine inhibitors in clinical trials: ETC-159 and WNT974. Preliminary data from 16 patients in the ongoing Phase 1a/b, first in human (FIH), dose escalation study of PORCN inhibitor, ETC-159, in advanced or metastatic solid tumours [NCT02521844] were first reported in 2017. At that time, the maximum tolerated dose (MTD) was 30mg every other day, with dose limiting toxicities of compression fractures and hyperbilirubinemia. Adverse events (>20%) included vomiting (32%), anorexia and fatigue (31%) dysgeusia and constipation (25%) Elevations of serum β-CTX, a marker of bone turnover, were observed (Ng et al 2017). Subsequently, prophylactic denosumab was introduced during the first 2 cycles. Data from the completed Phase 1, open-label trial of WNT974, administered in monotherapy have recently been published [NCT01351103] (Rodon et al 2021). In this study, 94 patients received oral WNT974 at doses of 5–30 mg once-daily, plus intermittent dosing schedules. AEs suspected to be related to study treatment were reported for 75 patients (80%), with the most common (≥20%) being dysgeusia (44 patients; 47%), decreased appetite (27 patients; 29%), and nausea (23 patients; 24%). Six patients (6.4%) experienced seven bone related disorders, five of which were suspected to be related to study treatment: osteoporosis, pathological fracture,

osteopenia, and two Grade 3 spinal fractures.

2.3.1.2 Risks of RXC004-Associated AEs

As described in section 4.4.1, RXC004 has been evaluated as a monotherapy in 23 patients in a Phase 1 monotherapy dose-escalation trial at doses of 0.5-10mg QD, in which doses of up to 2 mg QD were found to be tolerable and safe.

At doses up to and including 2 mg QD, the most common TRAEs of any grade were fatigue (10/20; 50%), nausea (7/20; 35%), anorexia (6/20 patients), dysgeusia (6/20; 30%) and vomiting (4/20; 20%).

Dysgeusia Events

In the Phase 1 study, RXC004-related dysgeusia was observed in 6/20 (30%) patients who received doses of up to 2 mg QD; 3/4 patients (75%) receiving 3 mg QD; and by the single patient (100%) who received 10 mg QD. This study protocol includes an assessment for the further characterisation of this event, and includes guidance for the management of dysgeusia (Appendix J). Guidance for dose modifications of RXC004 for all toxicities are provided in Section 6.5.

Colitis Events

In the Phase 1 study, events of intestinal inflammation (colitis, enteritis or enterocolitis) were observed in four patients who started treatment with RXC004 at doses of ≥3 mg QD and three were dose-limiting toxicities. CTCAE Grade 3 RXC004-related colitis occurred in the single patient who received 10 mg and CTCAE Grade 3 enteritis occurred in one patient who received RXC004 3 mg QD. CTCAE Grade 2 colitis also developed in two more patients who started treatment with 3 mg RXC004, both Grade 2 events presented during Cycle 2. Symptoms included abdominal pain, intermittent constipation, diarrhoea, nausea and/or vomiting. Blood and mucus in the stool were not apparent in any of the cases. Symptoms were usually accompanied by, and preceded by, a raised CRP. In two patients, the event recurred after initially responding to steroids, but responded again to further treatment.

Colitis events were not observed in any patients who commenced treatment with doses of RXC004 2 mg QD and lower in the Phase 1 study, and the 3 mg QD dose gave a disproportionately high exposure compared to 2 mg QD. However, at the time of publishing this protocol, a serious adverse event (SAE) of Grade 3 enteritis has been reported in 1 patient out of 12 patients dosed in the Phase 2 study RXC004/0002 and an SAE of Grade 3 colitis has been reported in 1 patient out of 21 patients dosed in this Phase 2 study (RXC004/0003). Both patients were receiving RXC004 2 mg QD. The enteritis and the colitis events were both considered by the Investigator as RXC004-related. Therefore, there is a potential risk for

colitis in patients receiving RXC004 as monotherapy, and in combination with pembrolizumab in this study.

Guidelines for the investigation and management of diarrhoea/colitis are provided in Appendix K. Guidance for dose modifications of RXC004 for all toxicities are provided in Section 6.5.

Colitis events are also defined as an Adverse Event of Potential Interest (AEPI) for RXC004, requiring additional details to be recorded on routine safety reporting.

Bone Events

Since Wnt inhibition both reduces bone formation and increases bone resorption, the concomitant use of the anti-resorbing agent, denosumab, is expected to prevent drug-induced bone loss, and this has been a successful approach in the Phase 1 study, along with patient selection, and monitoring. Patients with high risk of bone fractures are excluded in study protocols and participating patients will be monitored for bone turnover biomarkers and bone mineral density while on study.

In this study, patients will receive prophylactic denosumab (120 mg SC QM) along with vitamin D3 (cholecalciferol, 800 IU QD) and calcium (1000-1500 mg daily) supplements from the time of signing the ICF and throughout the study until discontinuation of RXC004.

Guidance for dose modifications of RXC004 and pembrolizumab for all toxicities are provided in Section 6.5. Bone-toxicity events are defined as an AEPI for RXC004, requiring additional details to be recorded on routine safety reporting.

Assessment of Potential for Other Risks

Potential for DDI with CYP 3A4 inhibitors

RXC004 has not shown the potential to induce or inhibit CYP enzymes or transporters at the dose to be investigated in this study but it is exclusively metabolised by CYP3A4 and as such has the potential for DDI with potent CYP inhibitors (which could increase levels of RXC004, leading to a higher risk of AEs). As such, strong and moderate CYP3A4 inhibitors are contraindicated in this protocol (see Appendix E). Patients with pancreatic and biliary tract cancers commonly require co-medications with analgesics, antacids, antibiotics, anti-emetics, anti-diabetic agents, anti-diarrhoeal drugs, anti-depressants, anxiolytic drugs, pancreatic enzyme replacements and other nutritional supplements. Some agents within these classes are CYP3A4 inhibitors.

Appendix E highlights the CYP 3A4 inhibitors which are also likely to be commonly used in CRC patients. These drugs should be avoided, and alternatives used wherever possible. If it is

not possible to use an alternative (e.g. if a specific antibiotic or anti-fungal treatment is needed), RXC004 should be interrupted.

Potential for QTc Prolongation

Based on pre-clinical data (hERG assay, ECG monitoring in 28-day GLP toxicology studies), RXC004 is not considered to have a significant potential to prolong the QTc interval. RXC004 did not lead to cardiac AEs including arrhythmias, or syncope in the Phase 1 study.

Triplicate ECGs will be collected in this other RXC004 studies so that the potential for QTc prolongation can be explored in future as part of a population PK analysis.

Potential for an Effect of Food on RXC004 Exposure

It is not yet known whether food may increase or decrease the exposure of RXC004. Until such data are generated, RXC004 must be given in a fasted state, as described in Section 5.6.2, and this is explained to patients in the Information Sheet.

Potential for Risks in Specific Patient Populations

A preliminary analysis of data from the Phase 1 study showed no effect of age, sex. BMI or race on RXC004 PK.

Pre-clinical development showed that RXC004 is exclusively metabolised by CYP3A4 and there was no renal clearance of RXC004. However, there is currently no information on the clearance of potential human metabolites of RXC004. While data are limited, the study inclusion criteria will restrict the use of RXC004 to patients with adequate renal and hepatic function.

More detailed information about the known and potential risks of RXC004 may be found in the most recent IB and Development Safety Update Report.

2.3.2 RXC004 Benefit Assessment

The benefit assessment for patients enrolled in Module 1 and 2 can be found in Sections 10.3.2 and 11.3.2, respectively.

2.3.3 Pembrolizumab Risks

In Module 3, patients will be treated with RXC004 in combination with pembrolizumab. For details of dose modification and toxicity management for immune-related AEs (irAEs) associated with pembrolizumab and infusion reactions related to pembrolizumab, see Appendix L 1 and L 2, respectively. The risk assessment for treatment with RXC004 in combination with pembrolizumab in Module 3 is provided in Section 12.3.1. Guidelines for the investigation and management of diarrhoea/colitis, which may occur with RXC004 or with

pembrolizumab, are provided in Appendix K.

The safety monitoring committee (SMC) will conduct a safety review of the combination data after [redacted] patients have received the combination of RXC004 and pembrolizumab for at least 1 cycle.

2.3.4 RXC004 Plus Pembrolizumab Benefit Assessment

The benefit assessment for patients enrolled in Module 3 is provided in Section 12.3.2.

2.3.5 Overall Benefit: Risk Conclusion

Considering the measures taken to minimise risk to patients participating in this study, the potential risks identified in association with study treatment are justified by the anticipated benefits that may be afforded to participants with Wnt pathway aberrantly activated advanced solid tumours.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the anti-tumour activity of RXC004 as monotherapy and as combination therapy	• 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 as monotherapy and as combination therapy	• 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 as monotherapy and as combination therapy	Maximum plasma concentration (C_{max}) after Dose 1, C_{max} at steady state, minimum observed plasma concentration (C_{min}) at steady state as well as other relevant parameters (e.g. t_{max}, $t½$, λz, $AUC_{0-\infty}$, CL/F, and Vz/F).
Safety	
To assess the safety and tolerability profile of RXC004 as monotherapy and as combination therapy	Incidence of AEs SAEs, dose reductions, interruptions and discontinuations, and assessment of dysgeusia.
Exploratory	
CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI

Objectives	Endpoints
CCI	CCI
CCI	CCI
CCI	CCI
CCI	
CCI	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	
CCI	CCI
CCI	CCI
	CCI

BOR, best overall response; CCI; CCI; CCI CCI; CCI, CCI, CCI; PFS, progression-free survival; PK, pharmacokinetic(s).

4 STUDY DESIGN

4.1 Overall Design

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

The study initially opened with RNF43 LoF mutation-positive PDAC (Module 1) and molecularly unselected BTC (Module 2) modules. Module 3, incorporated with protocol amendment 4, will investigate RXC004 in combination with pembrolizumab in BTC. Further modules (or cohorts within modules) evaluating the efficacy of RXC004 in other advanced solid tumours may be added at a later date.

The estimated number of patients to be enrolled is as follows:

- Module 1, CCI patients enrolled to achieve CCI evaluable patients
- Module 2:
  - Cohort 1: CCI patients enrolled to achieve CCI evaluable patients
  - Cohort 2: CCI patients enrolled to achieve CCI evaluable patients
- Module 3, CCI patients enrolled to achieve CCI evaluable patients

For the definition of an evaluable patient, see Table 14.

The primary objective of the study is to assess the preliminary efficacy of RXC004 in each module. This will be evaluated in terms of progression free survival (PFS) at 6 months in Modules 1 and 2, and in terms of ORR in Module 3. 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 [RECIST1.1]). Following radiological progression, patients will be followed-up for safety and survival.

The general study design is summarised in Figure 1.

4.2 Scientific Rationale for Study Design

The Wnt signalling pathway plays an important role in tumourigenesis (Zhan et al 2016) and in immune evasion (Goldsberry et al 2019) in many common cancers.

RNF43 is an integral membrane E3 ubiquitin ligase that promotes degradation of cell-surface Wnt receptors. Approximately 5-10% of all pancreatic cancers harbour a LoF RNF43 mutation (Jiang et al 2013, Bailey et al 2016 and Waddell et al 2015), which leads to increased Wnt receptors at the cell surface and hence elevated Wnt signalling.

Downstream Wnt pathway mutations are rare in biliary cancer, but patient samples have been shown to overexpress Wnt ligands. IHC of patient samples showed Wnt3a, Wnt5a, and Wnt7b were positive in 92.1%, 76.3%, and 100 % of 38 cholangiocarcinoma (CCA) tissues (Loilome et al 2014). In a separate study of 37 patients Wnt7B and Wnt10A mRNA was found to be significantly higher in CCA when compared to healthy tissue (Boulter et al 2015). High expression of Wnt5a was associated with worse prognosis (Loilome et al 2014).

PORCN is a membrane-bound protein-serine O-palmitoleoyltransferase which is required for the acetylation, activation and secretion of Wnt ligands. Blocking Wnt signalling with PORCN inhibitors has been shown to suppress the growth of BTC and RNF43-mutant pancreatic cancers in preclinical models (Madan et al 2016, Koo et al 2015, Boulter et al 2015, Noll et al 2016, Jiang et al 2013).

RXC004 is a potent and selective small molecule inhibitor of PORCN, which is currently being assessed in the Phase 1 RXC004/0001 trial (NCT03447470) for safety and tolerability in advanced malignancies. RXC004 warrants further development in advanced solid tumours with high Wnt signalling. This study initially opened with a RNF43 LoF mutation positive PDAC module (Module 1) and a BTC module (Module 2). An additional BTC module (Module 3) was added subsequently in protocol amendment 4.

Further modules evaluating the efficacy of RXC004 in other Wnt associated advanced solid tumours may be added at a later date.

4.3 Rationale for Study Endpoints

4.3.1 Primary Endpoint

The rationales for the primary study endpoints in Modules 1, 2, and 3 can be found in Sections 10.5.1, 11.5.1, and 12.5.1, respectively.

4.3.2 Secondary Endpoints

The rationales for the secondary study endpoints in Modules 1, 2, and 3 can be found in Sections 10.5.2, 11.5.2, and 12.5.2 respectively.

4.4 Justification for Dose

4.4.1 RXC004

Patients who enrol in this study to participate either in Module 1, or the first cohort of Module 2 will receive 2.0 mg RXC004 orally once a day in a fasted state. This dose was chosen using the predicted efficacious dose ranges from pre-clinical pharmacology models, pre-clinical and clinical target engagement assays, information from toxicology and toxicokinetic studies, and safety, efficacy and PK data from the Phase 1 study of RXC004 in patients with advanced solid tumours (NCT03447470).

Patients who enrol in the second cohort of Module 2 will receive a lower dose, RXC004 1 mg, dependent on emerging data from the RXC004 2 mg dose cohort. Selection of the RXC004 1 mg monotherapy dose for evaluation is based on target engagement assays, safety data (see Section 4.4.1.1), and efficacy and PK data (Section 4.4.1.3).

Patients who enrol in Module 3 will receive RXC004 1.5 mg QD in combination with pembrolizumab 400 mg IV infusion every 6 weeks (q6w). The RXC004 1.5 mg dose is supported by the available safety data for this dose given in combination with nivolumab in the Phase 1 study RXC004/0001 (NCT03447470). The safety review committee (SRC) agreed that RXC004 1.5 mg in combination with nivolumab is a tolerated dose at a meeting held on 07 July 2022, based on safety and PK data (see Section 4.4.1.2). The pembrolizumab dose and regimen is approved by the EMA for use in multiple cancer indications (KEYTRUDA SmPC).

4.4.1.1 RXC004 Clinical Safety Data (NCT03447470) - Monotherapy

As of 30 July 2021, 25 patients had received treatment with RXC004 monotherapy, which completed the module. This study opened in 2018 with a dose of RXC004 10 mg QD, but the dose was not tolerated in the first patient who developed Grade 3 diarrhoea, colitis and asymptomatic bone-fragility fractures in a thoracic vertebra and clavicle, which are on-target toxicities of Wnt pathway inhibitors. 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 study restarted the dose escalation on 18th March, 2019 with RXC004 0.5 mg QD.

As of 30 July 2021, 24 additional patients had been dosed with RXC004 monotherapy in Module 1 of the study at doses of 0.5 mg, 1 mg, 1.5 mg, 2 mg and 3 mg, a six-fold dose range. Six patients received treatment at highest declared tolerated dose (2 mg) – and all were evaluable for DLT analysis.

Table 1 ≥Grade 2 RXC004-related AEs, including DLTs, observed in DLT evaluable patients as of 30 July 2021 (Phase 1 study RXC004/0001, monotherapy)

Dose	Patients dosed	Patients evaluable for DLT	≥Grade 2 RXC004-related AEs in DLT evaluable[a] patients
0.5mg QD	4	3	**Tolerated dose** RXC004 related AEs ≥ CTCAE G2 (2/3 patients); G2 fatigue (1/3 patients) G2 increase in β-CTX (1/3 patients)
1mg QD	3	3	**Tolerated dose** RXC004 related AEs ≥ CTCAE G2 (1/3 patients); G2 fatigue (1/3 patients)

Dose	Patients dosed	Patients evaluable for DLT	≥Grade 2 RXC004-related AEs in DLT evaluable[a] patients
			G2 increase in β-CTX (1/3 patients) G2 loss of appetite (1/3 patients) G2 Nausea (1/3 patients)
1.5mg QD	7	6	**Tolerated dose** RXC004 related AEs ≥ CTCAE G2 (4/6 patients); G2 fatigue (4/6 patients)[b] G2 loss of appetite/anorexia (2/6 patients)[b] G2 Nausea (1/6 patients), G3 Nausea (1/6 patients)[b] G2 Dysgeusia (1/6 patients)[b] G2 increased AST (1/6 patients)[b] G2 decreased sodium (1/6 patients)[b] G3 diarrhoea (1/6 patients)[b] G3 vomiting (1/6 patients)[b] G3 weight loss (1/6 patients)[b]
2mg QD	6	6	**Tolerated dose** RXC004 related AEs ≥ CTCAE G2 (4/6 patients); G3 Pancreatitis (1/6 patients) [**DLT**] G2 Diarrhoea (2/6 patients) G2 Dysgeusia (1/6 patients)[b]
3mg QD	4	4	**Non-tolerated dose** RXC004 related AEs ≥ CTCAE G2 (4/4 patients); G2 Fatigue (1/4 patients)[b] G2 Nausea (1/4 patients)[b] G2 Constipation (1/4 patients)[b] G2 Anorexia (2/4 patients)[b] G2 Colitis (2/4 patients)[b] [**DLT**] G2 Dysgeusia (1/4 patients)[b] G3 Enteritis (1/4 patients) [**DLT**] G2 hyponatremia (1/4 patients) G2 Humerus fracture (1/4 patients) G5 Subdural Hematoma (1/4 patients)
10mg QD	1	1	**Non-tolerated dose** One **DLT** – G3 Diarrhoea. G3 proctitis, G2 enterocolitis, dysgeusia and fragility bone fractures also reported for this patient

[a] The DLT assessment period runs from the start of dosing with RXC004 (Cycle 0 Day 1) up to Cycle 1 Day 21. To be evaluable for DLT assessment patient must had received at least 66% of the intended dose of RXC004 during Cycle 1 or have experienced a DLT event in the assessment period

[b] The start date of one or more events was outside of the DLT period. However, AEs occurring in Cycle 2 and beyond which meet the definition of a DLT or are considered clinically significant may also be considered by the Safety Review Committee, when making dose escalation decisions.

AE, adverse event; DLT, dose-limiting toxicity; QD, once daily.

No DLTs were observed in the patients dosed in the first three cohorts since the study was restarted (RXC004 doses from 0.5mg to 2mg). At the 3mg dose level, two DLTs of colitis and enteritis were observed in 2/4 (50%) evaluable patients, which led to the SRC declaring RXC004 3 mg QD as non-tolerated.

Denosumab (XGEVA™ - 120 mg s.c. once every month) was administered prophylactically from Cycle 0 to all patients from cohort 3 (1.5mg RXC004) onwards, to maximise bone safety.

A summary of the TEAEs, regardless of causality, reported for RXC004 monotherapy in the Phase 1 study RXC004/0001 (NCT03447470) up to 30 July 2021 is included in Table 2 below.

Table 2 Summary of TEAEs (Phase 1 study RXC004/0001, monotherapy)

Number of patients with TEAE	0.5 mg; N=4 n (%)	1.0 mg; N=3 n (%)	1.5 mg; N=7 n (%)	2.0 mg; N=6 n (%)	3.0 mg; N=4 n (%)	10.0 mg; N=1 n (%)	Overall; N=25 n (%)
Any TEAE	4 (100)	3 (100)	7 (100)	6 (100)	4 (100)	1 (100)	25 (100)
Any Treatment-Related TEAE	4 (100)	3 (100)	5 (71)	5 (83)	4 (100)	1 (100)	22 (88)
TEAE ≥Grade 3	0 (0)	1 (33)	6 (86)	1 (17)	3 (75)	1 (100)	12 (48)
Treatment-Related TEAE ≥Grade 3	0 (0)	0 (0)	2 (29)	1 (17)	1 (25)	1 (100)	5 (20)
Serious TEAE	0 (0)	1 (33)	5 (71)	1 17)	3 (75)	1 (100)	11 (44)
Serious Treatment-Related TEAE	0 (0)	0 (0)	1 (14)	0 (0)	2 (50)	1 (100)	4 (16)
TEAE Leading to Discontinuation of Study Treatment	1 (25)	0 (0)	2 (29)	0 (0)	2 (50)	1 (100)	6 (24)
Treatment-Related TEAE Leading to Discontinuation of Study Treatment	1 (25)	0 (0)	2 (29)	0 (0)	2 (50)	1 (100)	6 (24)
TEAE Leading to Dose Modification	0 0)	1 (33)	3 (43)	2 (33)	2 (50)	1 (100)	9 (36)
TEAE Leading to Death	0 (0)	0 (0)	1 (14)	0 (0)	1 (25)	0 (0)	2 (8)

The most common TEAEs and TRAEs (occurring in ≥20% patients) are summarised in Table 3 and Table 4. The most frequently occurring TEAEs were fatigue (64%), nausea (56%), decreased appetite (48%), vomiting (40%), dysgeusia (40%), diarrhoea (32%), AST increased (28%), anaemia (20%), and constipation (20%).

Table 3 Most common (occurring in ≥20% patients) TEAEs in Phase 1 study RXC004/0001 Module 1 (monotherapy)

Preferred Term; n (%)	0.5 mg; N=4	1.0 mg; N=3	1.5 mg; N=7	2.0 mg; N=6	3.0 mg; N=4	10.0 mg; N=1	Overall; N=25
Patients with any TEAEs	4 (100)	3 (100)	7 (100)	6 (100)	4 (100)	1 (100)	25 (100)
Fatigue	2 (50)	2 (67)	6 (86)	3 (50)	2 (50)	1 (100)	16 (64)
Nausea	2 (50)	2 (67)	5 (71)	1 (17)	3 (75)	1 (100)	14 (56)
Decreased appetite	1 (25)	2 (67)	3 (43)	2 (33)	3 (75)	1 (100)	12 (48)
Vomiting	0 (0)	2 (67)	4 (57)	2 (33)	1 (25)	1 (100)	10 (40)
Dysgeusia	0 (0)	0 (0)	2 (29)	4 (67)	3 (75)	1 (100)	10 (40)
Diarrhoea	1 (25)	2 (67)	3 (43)	1 (17)	0 (0)	1 (100)	8 (32)
AST increased	1 (25)	0 (0)	3 (43)	1 (17)	1 (25)	1 (100)	7 (28)
Anaemia	1 (25)	2 (67)	2 (29)	0 (0)	0 (0)	0 (0)	5 (20)
Constipation	0 (0)	0 (0)	1 (14)	1 (17)	2 (50)	1 (100)	5 (20)

The most common RXC004-related AEs reported were: fatigue (52%), nausea (44%), decreased appetite (40%), dysgeusia (40%) and vomiting (24%). At doses ≤2 mg QD, the most common TRAEs were fatigue (10/20 patients), nausea (7/20), anorexia (6/20), dysgeusia (6/20), and vomiting (4/20). No Grade 4/5 TRAEs or bone-fragility events were reported at any dose levels ≤2 mg QD. Only dysgeusia appeared to be dose-related.

Table 4 Most Common (Occurring in ≥20% patients) TRAEs in Phase 1 study RXC004/0001 Module 1 (monotherapy)

Preferred Term	0.5 mg; N=4 n (%)	1.0 mg; N=3 n (%)	1.5 mg; N=7 n (%)	2.0 mg; N=6 n (%)	3.0 mg; N=4 n (%)	10.0 mg; N=1 n (%)	Overall; N=25 n (%)
Patients with any TRAEs	4 (100)	3 (100)	5 (71)	5 (83)	4 (100)	1 (100)	22 (88)
Fatigue	2 (50)	1 (33)	4 (57)	3 (50)	2 (55)	1 (100)	13 (52)
Nausea	1 (25)	2 (67)	3 (43)	1 (17)	3 (75)	1 (100)	11 (44)
Decreased appetite	1 (25)	1 (33)	2 (29)	2 (33)	3 (75)	1 (100)	10 (40)
Dysgeusia	0 (0)	0 (0)	2 (29)	4 (67)	3 (75)	1 (100)	10 (40)
Vomiting	0 (0)	1 (33)	2 (29)	1 (17)	1 (25)	1 (100)	6 (24)

Five patients reported nine CTCAE Grade 3 events that were assessed by the Investigator as possibly or probably related to RXC004, and these patients all received doses of ≥1.5 mg. These events were: weight loss (one patient, 1.5 mg); nausea, vomiting and diarrhoea (all in one patient, 1.5 mg); pancreatitis (one patient, 2 mg); enteritis (one patient, 3 mg) and diarrhoea, proctitis and hyponatraemia (all in one patient, 10 mg). No Grade 4 events were reported. Two Grade 5 events were reported: COVID-19 infection (one patient, 1.5 mg, not related to RXC004) and sub-dural haematoma following a fall (one patient, 3 mg) assessed as possibly related to RXC004). See Table 1.

A total of 16 SAEs were reported in 11 patients. Nine of the 16 SAEs reported were assessed by the Investigator and the Sponsor as unrelated to the RXC004 . These were: gastroenteritis viral (Grade 3, one patient, 1 mg), *Escherichia* UTI (Grade 3, one patient, 1.5 mg), pulmonary haemorrhage (Grade 1, one patient, 1.5 mg), melaena (two SAEs in one patient at 1.5 mg – one Grade 1 then other Grade 3 – both due to a new primary malignancy), small intestinal obstruction (Grade 3, one patient 1.5 mg), COVID-19 (Grade 5, 1 patient, 1.5 mg), stoma-site infection (Grade 2, one patient, 2 mg) and biliary-tract infection (Grade 3, one patient, 3 mg). seven SAEs (which occurred in four patients) were assessed by the Investigator as possibly or probably related to RXC004 and are described below:

- Two SAEs of NCI CTCAE Grade 2/3 diarrhoea that occurred in one patient at RXC004 10 mg QD (before the study was re-started) were both assessed as probably related to RXC004 and led to discontinuation of study drug. The events subsequently resolved/recovered and RXC004 10 mg QD was declared by the SRC to be not tolerated.
- One SAE of NCI CTCAE Grade 3 diarrhoea that occurred at RXC004 1.5 mg was assessed as probably related to RXC004 and led to discontinuation of study drug. The

event was also associated with a *Clostridium difficile* infection and subsequently resolved/recovered.

- One SAE of NCI CTCAE Grade 2 colitis that occurred at RXC004 3 mg QD was assessed as probably related to RXC004. The event subsequently resolved and the patient continued study treatment at a lower dose (RXC004 1.5 mg). The RXC004 3 mg QD dose was subsequently declared by the SRC not to be tolerated.
- One SAE of NCI CTCAE Grade 3 enteritis that occurred at RXC004 3 mg QD was assessed as probably related to RXC004. This patient also had a SAE of NCI CTCAE Grade 2 humerus fracture (following a fall while hospitalised for enteritis), which was assessed as probably related to RXC004. The enteritis and fracture events were both unresolved at the time that the patient subsequently died due to a CTCAE Grade 5 sub-dural hematoma (following a fall). The sub-dural hematoma was assessed by the Investigator as possibly related to RXC004 due to unknown mechanism as an association between the study drug and potential factors that could have contributed to this event, such as coagulation, had not been ruled out at the time of death. The RXC004 3 mg QD dose was subsequently declared by the SRC not to be tolerated.

4.4.1.2 RXC004 Safety Data in Combination with Nivolumab

As of 01 July 2022, 13 patients have received RXC004 in combination with nivolumab 480 mg Q4W at doses of RXC004 1 mg and 1.5 mg QD in Module 2 of the ongoing Phase 1 study RXC004/0001. Eight of these patients received treatment at the highest declared tolerated dose (RXC004 1.5 mg). Treatment related AEs of CTCAE ≥ Grade 2 reported in DLT-evaluable patients are summarised in Table 5.

Overall, the AE profile of the RXC004 1.5 mg dose in combination with nivolumab is similar to the RXC004 2 mg monotherapy dose. More patients who received the 1.5 mg dose had treatment related AEs of Grade 2 or higher (4/6) than patients who received the 1 mg dose (2/5). One patient who received 1.5 mg in combination had drug-induced liver injury (DILI), which was considered drug-related and a DLT.

The SRC determined at a meeting held on 07 July 2022, that both RXC004 1 mg and 1.5 mg QD in combination with nivolumab are tolerated doses. A decision was made not to further escalate the dose in the study, based on the safety and PK profiles of the 1.5 mg dose, as the combination of RXC004 2 mg with nivolumab was anticipated to lead to slightly higher exposure and potentially more AEs than the 2 mg monotherapy dose.

Table 5 Treatment-related AEs Grade 2 or higher including DLTs, observed in DLT evaluable patients as of 01 July 2022, Phase 1 study RXC004/0001 Module 2 (RXC004 + nivolumab)

Dose	Number of patients dosed	Patients evaluable for DLT	Study treatment-related AEs, CTCAE ≥ Grade 2 in DLT-evaluable [a] patients
1.0 mg QD RXC004 + nivolumab 480 mg q4w	5	5	**Tolerated dose** Events ≥ Grade 2 in DLT-evaluable patients (2/5 patients): G2 back pain (1/5 patients) [b] G2 nausea (1/5 patients) [b] G2 fatigue (1/5 patients) [c] G2 poor appetite (1/5 patients) [c] G3 fatigue (1/5 patients) [b]
1.5 mg QD RXC004 + nivolumab 480 mg q4w	8	6 [e]	**Tolerated dose** Events ≥ Grade 2 in DLT evaluable patients (4/6 patients): G2 dysgeusia (2/6 patients) [b] G2 diarrhoea (1/6 patients) [b] G2 diarrhoea (1/6 patients) [c] G2 reduced appetite (1/6 patients) [b] G2 nausea (1/6 patients) [b] G2 constipation (1/6 patients) [d] G2 anorexia (1/6 patients) [b] G2 increased total bilirubin (1/6 patients) [b] G2 high total bilirubin (1/6 patients) [b] G3 drug-induced liver injury (1/6 patients) **[DLT]** [c]

[a] The DLT assessment period ran from the start of dosing with RXC004 (Cycle 0 Day 1) up to Cycle 1 Day 28. To be evaluable for DLT assessment patient must have received ≥ 66% of the intended dose of RXC004 and all of the nivolumab infusion during Cycle 1, or experienced a DLT event in the assessment period.

[b] Related to RXC004.

[c] Related to RXC004 and nivolumab.

[d] Related to nivolumab

[e] Two of the 8 patients who received RXC004 1.5 mg in combination with nivolumab discontinued prior to the end of Cycle 1 without meeting DLT criteria, and were replaced.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; q4w, every 4 weeks; QD, once daily.

Table 6 summarises the TEAEs reported with RXC004 + nivolumab by category.

Table 6 Summary of TEAEs, as of 01 July 2022, Phase 1 study RXC004/0001 Module 2 (RXC004 + nivolumab)

Category of TEAE	Number (%) of patients		
	RXC004 1.0 mg + nivolumab (N = 5)	RXC004 1.5 mg + nivolumab (N = 8)	Overall (N = 13)
TEAE	5 (100)	8 (100)	13 (100)
Treatment-related TEAE	5 (100)	8 (100)	13 (100)
TEAE ≥ Grade 3	3 (60)	4 (50)	7 (54)
Treatment-related TEAE ≥ Grade 3	1 (20)	3 (38)	4 (31)
TEAE ≥ Grade 4	0 (0)	0 (0)	0 (0)
Serious TEAE	3 (60)	3 (38)	6 (46)
Serious treatment-related TEAE	0 (0)	1 (13)	1 (8)
TEAE leading to discontinuation of study treatment (RXC004)	0 (0)	2 (25)	2 (15)
Treatment-related TEAE leading to discontinuation of study treatment	0 (0)	2 (25)	2 (15)
TEAE leading to RXC004 dose modification	2 (40)	5 (63)	7 (54)
Dose reduced	0 (0)	1 (13)	1 (8)
Dose interrupted	2 (40)	5 (63)	7 (54)
TEAE leading to death	0 (0)	0 (0)	0 (0)
TEAE of dose-limiting toxicity	0 (0)	1 (13)	1 (8)

AEs were coded using MedDRA Version 24.1. A TEAE was an AE with onset on or after date of first dose of study treatment and within 30 days of last dose.
Treatment-related AE was an AE that had relationship to study drug designated by the investigator as Possibly Related or Probably Related.
Treatment-Related: AEs related to RXC004 and/or nivolumab. If the relationship to RXC004 or nivolumab was missing, the event was conservatively treated as related to the corresponding study treatment.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

The most common TEAEs (that were reported by more than one patient) are summarised by RXC004 dose level and overall in Table 7. The most common TEAEs were decreased appetite, fatigue, and nausea which were all reported for 6 patients each (46%).

Table 7 Most common TEAEs, as of 01 July 2022, Phase 1 study RXC004/0001 Module 2 (RXC004 + nivolumab)

Preferred term	Number (%) of patients		
	RXC004 1.0 mg QD + nivolumab (N = 5)	RXC004 1.5 mg QD + nivolumab (N = 8)	Overall (N = 13)
Patients with any TEAEs	**5 (100)**	**8 (100)**	**13 (100)**
Decreased appetite	2 (40)	4 (50)	6 (46)
Fatigue	3 (60)	3 (38)	6 (46)
Nausea	2 (40)	4 (50)	6 (46)
Dysgeusia	1 (20)	4 (50)	5 (38)
Constipation	2 (40)	2 (25)	4 (31)
Headache	2 (40)	2 (25)	4 (31)
Weight decreased	1 (20)	3 (38)	4 (31)
Abdominal distension	1 (20)	2 (25)	3 (23)
Blood bilirubin increased	0 (0)	3 (38)	3 (23)
Pruritus	1 (20)	2 (25)	3 (23)
Urinary tract infection	0 (0)	3 (38)	3 (23)
Abdominal pain	0 (0)	2 (25)	2 (15)
Alanine aminotransferase increased	0 (0)	2 (25)	2 (15)
Aspartate aminotransferase increased	1 (20)	1 (13)	2 (15)
Back pain	1 (20)	1 (13)	2 (15)
Blood alkaline phosphatase increased	0 (0)	2 (25)	2 (15)
Diarrhoea	0 (0)	2 (25)	2 (15)
Hyperthyroidism	1 (20)	1 (13)	2 (15)
Vomiting	0 (0)	2 (25)	2 (15)

QD, once daily; TEAE, treatment-emergent adverse event.

The most common AEs (reported by more than one patient) related to study treatment (RXC004 or nivolumab) are summarised in Table 8. All 13 patients had at least one AE related to study treatment; the most common treatment-related AEs were nausea (46%), dysgeusia (38%), and fatigue (38%). With the exception of fatigue, all of these events were more frequently observed at the 1.5 mg dose than the 1 mg dose level. Dysgeusia is considered to be an on-target effect of Wnt inhibition.

Table 8 Most common AEs considered related to RXC004 or nivolumab, as of 01 July 2022, Phase 1 study RXC004/0001 Module 2 (RXC004 + nivolumab)

Preferred term	Number (%) of patients		
	RXC004 1.0 mg QD + nivolumab (N = 5)	RXC004 1.5 mg QD + nivolumab (N = 8)	Overall (N = 13)
Patients with any TRAEs	**5 (100)**	**8 (100)**	**13 (100)**
Nausea	2 (40)	4 (50)	6 (46)
Dysgeusia	1 (20)	4 (50)	5 (38)
Fatigue	2 (40)	3 (38)	5 (38)
Decreased appetite	1 (20)	3 (38)	4 (31)
Weight decreased	1 (20)	3 (38)	4 (31)
Blood bilirubin increased	0 (0)	3 (38)	3 (23)
Alanine aminotransferase increased	0 (0)	2 (25)	2 (15)
Aspartate aminotransferase increased	1 (20)	1 (13)	2 (15)
Constipation	1 (20)	1 (13)	2 (15)
Diarrhoea	0 (0)	2 (25)	2 (15)
Hyperthyroidism	1 (20)	1 (13)	2 (15)
Pruritus	1 (20)	1 (13)	2 (15)

QD, once daily; TRAE, treatment-related adverse event.

Three patients had CTCAE Grade 3 events that were assessed by the Investigator as possibly or probably related to RXC004: Grade 3 fatigue was reported by one patient who received RXC004 1 mg + nivolumab and one patient who received RXC004 1.5 mg. One patient who received RXC004 1.5 mg had Grade 3 events of aspartate aminotransferase increased, blood alkaline phosphatase increased, and DILI, which were considered to be related to both RXC004 and nivolumab. No other events of DILI were reported in either Module 1 or Module 2. A fourth patient had a Grade 3 event of anaemia with missing relationship details..

In total, 11 treatment-emergent SAEs were reported in 6 patients. Ten of the 11 SAEs reported were assessed by the Investigator and the Sponsor as unrelated to RXC004. These were as follows: infection (NOS), left leg weakness, and infection (all reported in one patient at 1 mg); kidney infection and liver pain (in one patient at 1 mg), and 2 events of ascites (in one patient at 1 mg); diarrhoea (in one patient at 1.5 mg); and chest infection and pneumonia (in one patient at 1.5 mg).

One SAE was assessed as being related to RXC004 and nivolumab: this was Grade 3 DILI in a patient who had colorectal cancer with liver metastases, and was reported on Cycle 1 Day 17. The event was considered to be a DLT, and study treatment was permanently discontinued. The liver function tests subsequently returned to baseline. The patient

subsequently died due to disease progression. No other events of DILI were reported in either Module 1 or Module 2.

4.4.1.3 RXC004 Pharmacokinetic Profile

The data from the ongoing Phase 1 study (NCT03447470) have characterised the PK of RXC004 monotherapy in patients following single and multiple oral doses ranging from 0.5 mg to 10 mg, and in combination with standard dose nivolumab at doses of RXC004 1 mg and 1.5 mg.

RXC004 was rapidly absorbed following oral dosing in fasting conditions, with a peak plasma concentration observed typically after 1-2 hours post-dose and eliminated with a half-life of approximately CCI hours. The exposures achieved in patients dosed with 0.5mg-2mg were broadly dose proportional and predictable from the exposure observed in the patient dosed at 10mg in terms of half-life, C_{max}, C_{min} and AUC. There was limited accumulation to steady state and it is in line with expectations from the measured half-life. The 3 mg dose C_{max}, C_{min} and AUC were all disproportionately high compared to the 2 mg dose, giving an estimated CCI in exposure for the 50% rise in dose.

There was little difference in RXC004 plasma exposure between monotherapy and combination therapy on Cycle 0 Day 1. On Cycle 1 Day 15, the steady state RXC004 plasma exposure appeared to be slightly greater on combination therapy compared with monotherapy, although patient numbers are small. The mechanism for a potential small increase in exposure when RXC004 is given with nivolumab is unclear since a PK interaction with a monoclonal antibody is unlikely, but an increase in bioavailability cannot be ruled out.

The plasma exposure of RXC004 when given at 1.5 mg in combination with nivolumab was no greater than that observed at 2 mg monotherapy and was around CCI than that observed at 3 mg monotherapy.

The steady state PK parameters of RXC004 from Study RXC004/0001, for RXC004 monotherapy and in combination with nivolumab are summarised in Table 9.

Table 9 Steady state pharmacokinetic parameters of RXC004, as of 01 July 2022, Phase 1 Study RXC004/0001, RXC004 monotherapy and combination with nivolumab)

Parameter (units)		RXC004 monotherapy				RXC004 in combination with nivolumab	
		1 mg	1.5 mg	2 mg	3 mg	1 mg	1.5 mg
C_{min} (ng/mL)	N	3	6	4	4	4	4
	Geometric mean (%CV)	7.15 (120)	12.6 (142)	26.8 (134)	73.1 (46.8)	8.62 (163)	13.6 (48.4)
T_{max} (h)	N	3	6	5	4	5	6
	Median (min – max)	1.00 (1–2.00)	2.00 (1.00–4.00)	1.00 (0.5–2.00)	0.75 (0.5-2.00)	2.0 (0.5-6.0)	1.5 (0.5-2.00)
C_{max} (ng/mL)	N	3	6	5	4	5	5
	Geometric mean (%CV)	42.4 (89.1)	56.6 (53.7)	68.5 (61.6)	220 (36.3)	58.2 (46.3)	76.4 (57.6)
AUC_{0-24} (h*ng/mL)	N	3	6	4	4	5	5
	Geometric mean (%CV)	392 (42)	630 (76)	931 (61.1)	2340 (32.5)	544 (65.5)	706 (40.1)

AUC_{0-24}, area under the plasma concentration-time curve from zero to 24 hours; C_{max}, maximum observed plasma concentration, C_{min}, minimum observed plasma concentration across the dosing interval; %CV, coefficient of variation; T_{max}, time to maximum plasma concentration.

4.4.1.4 RXC004 Pharmacodynamic and Efficacy Data

In pre-clinical pharmacology models, RXC004 demonstrated anti-tumour activity at steady state C_{min} exposures of between CCI and CCI fold IC_{50}, with evidence of improved efficacy at higher doses. The target human exposure to achieve monotherapy efficacy is a C_{min} value of CCI-fold IC_{50}.

Pharmacodynamic effects (>50% reduction in AXIN2 expression in skin) were observed in patients who achieved C_{min} exposure of > CCIfold IC_{50}.

As of 30 July 2021, 5/18 evaluable patients in the monotherapy module, with at least 2 scheduled RECIST1.1 scans had achieved durable SD of 10 weeks or longer – 1 patient dosed at 1.0mg QD (RNF43 LoF mCRC), 2 patients dosed at 1.5mg (CCA and RSPO fusion mCRC) and 2 patients dosed at 3mg (CCA and thymus cancer. The CCA patient had a dose reduction to 1.5mg RXC004 after experiencing colitis). Of note all 5 patients who achieved SD had a type of cancer in which RXC004 is most likely to demonstrate clinical benefit based on its mechanism of action. These selected tumour types are CRC or PDAC with a RNF43 LoF mutation or RSPO fusion, or BTC or thymus cancer, both of which are reported to have high Wnt ligand activity (Boulter et al 2015, Loilome et al 2014, Vodicka et al 2020). All patients with RECIST stable disease also achieved C_{min} exposures of CCI-fold IC_{50}.

Efficacy data for the combination of RXC004 + nivolumab in Module 2 are not yet available.

4.4.1.5 RXC004 2 mg Monotherapy Dose

Based on all available information, patients who enrol in this study and participate in either Module 1 or in Cohort 1 of Module 2 will receive 2.0 mg RXC004 orally QD.

The 2 mg QD dose was both tolerable and able to consistently deliver C_{min} values of CCI-fold IC_{50} in all patients, whereas the 1.0 mg and 1.5 mg QD doses did not consistently achieve the target C_{min} values of CCI fold IC_{50} in all patients.

The 2 mg dose has been selected for Phase 2 development as the optimal dose to demonstrate an efficacy signal in patients with genetically selected tumours and to allow for potential dose reductions to manage AEs.

4.4.1.6 RXC004 1 mg Monotherapy Dose

Patients who participate in Cohort 2 of Module 2 will receive RXC004 1.0 mg orally QD. The purpose of this cohort is to further characterise the dose-response relationships for activity and safety and to support the optimal dosage(s) for future clinical development.

In the Phase 1 study, the dosing cohorts were small (see Section 4.4.1.1) and patients were not selected for having Wnt ligand-dependent tumours. The median RXC004 exposure was short (approximately 7 weeks); thus, the AEs described in Section 4.4.1.1 were generally observed during the first 2 treatment cycles. Of the observed AEs, 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 2 mg cohort reported dysgeusia within the first 2 treatment cycles. Cohort 2 of Module 2 will explore whether the lower dose of 1 mg has the potential to deliver clinical anti-tumour activity in patients with BTC, a Wnt ligand-dependent tumour, and whether this lower dose has the potential to reduce incidence of treatment related toxicities such as dysgeusia. The 1.5 mg dose was not selected for this purpose because the PK profiles of the 1.5 mg dose and 2 mg dose show considerable overlap.

Initiation of this lower dose cohort will depend on emerging data from the RXC004 2 mg dose cohort. Should the 2 mg dose fail to show any anti-tumour activity in Cohort 1 that warrants further investigation (as per Section 11.9.1), then this lower dose cohort (Cohort 2 of Module 2) will not open unless the SMC consider that the tolerability of the 2 mg QD dose has compromised its ability to show efficacy.

4.4.1.7 RXC004 1.5 mg Dose in Combination with Pembrolizumab

Patients who participate in Module 3 will receive RXC004 1.5 mg orally QD, in combination with pembrolizumab 400 mg IV infusion q6w. Justification for the choice of RXC004 doses and regimens is provided in Section 4.4.1. Justification for the pembrolizumab dose and regimen is provided in Section 12.5.3.

4.5 End of Study Definition

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

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

The Sponsor may terminate this study at any time for reasons that include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Inability to complete the trial in a meaningful timeframe due to a lack of recruitment.
- A decision on the part of the Sponsor to modify/suspend or discontinue development of the drug.

5 STUDY POPULATION

The study will recruit male or female patients aged 18 years or older with histologically documented, advanced solid tumours that have progressed after standard of care treatment for advanced (unresectable)/metastatic disease (which varies according to the specific module defined patient population), and have a minimum life expectancy of 12 weeks.

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

5.1 Core Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be ≥18 years of age at the time of signing the informed consent.
2. Ability to give written informed consent and capable of understanding the protocol requirements listed in the informed consent form (ICF) and in this protocol. Written informed consent must be obtained prior to performing any protocol-related procedures, including screening evaluations. Participants must be willing and able to comply with the study protocol procedures and restrictions.
3. At least one lesion that is measurable by RECIST 1.1 at baseline (within 6 weeks prior to start of study treatment). The measurable lesion must not be chosen for the mandatory paired biopsies.
4. Mandatory paired biopsies; Patients must have at least one lesion suitable for biopsy at screening (which must not be a target lesion for RECIST 1.1) and be willing to provide mandatory tumour biopsy samples as follows:
   (i) Baseline* (mandatory and must be performed before study treatment commences, except in exceptional circumstances where biopsy is not technically feasible. All patients without a baseline sample must be approved by Sponsor before starting study treatment as a minimum number of 5 paired biopsies per module are required to achieve the study objectives).
   (ii) On treatment at C1D15 (+ 7 days). The C1D15 tumour biopsy is also mandatory and should be performed unless the investigator judges that this biopsy is contraindicated (high risk biopsy as defined by ASCO guidelines: Levit et al 2019).

   * Archival biopsy (ideally from the same site that C1D15 biopsy will be taken) that were taken after completion of all prior standard of care treatments will be accepted as a baseline biopsy.

5. Adequate organ and marrow function [Note: for Module 3 the samples must be collected within 10 days prior to the start of study treatment]:

- AST/ALT ≤ 3× ULN for patients with no Liver Metastasis or AST/ALT ≤ 5× ULN for patients with Liver Metastasis. [Note: for Module 3, AST/ALT must be ≤ 2.5× ULN for patients with no Liver Metastasis]
- Total Bilirubin ≤ 1.5× ULN (with the exception of patients with Gilberts disease [≤ 3 x ULN])
- Serum Creatinine ≤ 1.5× ULN
- ANC ≥ 1.5× 10^9/L
- Platelets > 100× 10^9/L
- Hb > 9g/dL (with or without transfusion support). [Note: for Module 3, this criterion must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).]
- Calculated CrCL ≥ 60 mL/min as determined by Cockcroft Gault (using actual body weight).

  Males:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  Females:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

6. Female patients of childbearing potential must have a negative pregnancy test prior to start of dosing. See the Schedules of Assessments for the timings of the required tests. [Note: in Module 3, a woman of child-bearing potential who has a positive urine pregnancy test within 72 hours prior to start of study treatment will be excluded from the study.]

7. Female patients of childbearing potential and male patients with female partners of childbearing potential must agree to use a highly effective method of contraception during the study from the time of treatment initiation, and for at least 5 months after the last dose of study drug. See Section 5.6.1 for details of acceptable methods of contraception

5.2 Module 1 (PDAC) Specific Inclusion Criteria

Participants are eligible to be included in Module 1 if in addition to the Core Inclusion Criteria all of the following criteria apply:

8. Histological documentation of advanced (unresectable)/metastatic (Stage III/IV) pancreatic ductal adenocarcinoma, with documented loss of function tumour mutation in RNF43 from centralised genetic pre-screening activities or from a recognised panel in agreement with sponsor*. Please see Section 5.8 and Appendix F for more details.

   *CCI [redacted]

   CCI [redacted]

   CCI [redacted]

9. Patients must have received one prior systemic treatment for advanced (unresectable)/metastatic pancreatic ductal adenocarcinoma (Stage III/IV), with clear evidence of radiological disease progression. Patients with advanced disease may also have received prior adjuvant therapy. Patients that have radiologically progressed during or within 6 months of completion of systemic adjuvant chemotherapy may also be allowed (as progression within 6 months of adjuvant treatment may be considered as first-line chemotherapy for metastatic disease).
10. Patients must be enrolled and receive first dose of study treatment within 6 weeks of radiologically confirmed progression. In exceptional circumstances, Sponsor approval for patients to be enrolled within 8 weeks of radiologically confirmed progression may be given (exceptional circumstances may include logistical reasons or patients with indolent, oligometastatic disease).
11. Karnofsky performance status ≥70 with no deterioration in the 2 weeks prior to first dose and an estimated life expectancy of greater than 12 weeks (See Appendix G).

5.3 Module 2 and Module 3 (BTC) Specific Inclusion Criteria

Participants are eligible to be included in Module 2 or Module 3 if in addition to the Core Inclusion Criteria all of the following criteria apply:

12. Histological documentation of advanced (unresectable)/metastatic (Stage III/IV) BTC (intrahepatic or extrahepatic cholangiocarcinoma, ampulla of Vater, or gallbladder cancer).
13. Patients must have received one prior systemic treatment for advanced (unresectable)/metastatic Biliary Tract Cancer (BTC), with clear evidence of radiological disease progression (these patients are allowed to have received prior immunotherapy). Patients may also have received prior adjuvant therapy, and additionally, patients that have radiologically progressed during or within 6 months of completion of systemic adjuvant chemotherapy may also be allowed (as progression within 6 months of adjuvant treatment may be considered as first-line chemotherapy for unresectable/metastatic disease).
14. Patients must be enrolled and receive first dose of study treatment within 6 weeks of radiologically confirmed progression. In exceptional circumstances, Sponsor approval

for patients to be enrolled within 7 weeks of radiologically confirmed progression may be given (exceptional circumstances may include logistical reasons or patients with indolent, oligometastatic disease).

15. ECOG status 0 or 1 with no deterioration in the 2 weeks prior to study day 1 and an estimated life expectancy of greater than 12 weeks (See Appendix G).

5.4 Core Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior therapy with a compound of the same mechanism of action as RXC004.
2. Patients at higher risk of bone fractures, including;
    a) Patients with Vitamin D [25(OH)D_3] deficiency defined as < 30 nmol/L (< 12 ng/mL). [Note - Patients who fail on this criterion can be given supplementation and be retested within the screening window]
    b) Patients with a corrected serum calcium level of < 2 mmol/L and serum magnesium level of < 0.60 mmol/L.
    c) Patients with osteoporosis (as defined by a T-score of < -2.5 at any of the 3 following sites, all of which must be assessed: L/R total hip, L/R femoral neck, lumbar spine (L1-4) by DEXA scan) or history of fragility fractures (any fracture occurring with low-level trauma or as a result of falling < standing height)
    d) Patients with ongoing or a history of clinically significant hyperparathyroidism, Pagets disease or osteomalacia. Patients with a prior diagnosis of hyperparathyroidism, Pagets disease or osteomalacia, considered by the investigator to have no increased bone fragility risk, may be included.
3. Any known uncontrolled inter-current illness or persistent clinically significant toxicity related to prior anti-cancer treatment (as assessed by the Investigator) which in the investigator's opinion makes it undesirable for the patient to participate in the study.
4. Patients who have any history of an active (requiring treatment) other malignancy (except any in-situ carcinoma, non-melanoma skin carcinoma, and early prostate cancer with a normal PSA) within 2 years of study entry.
5. Patients with known or suspected brain metastases
6. Use of anti-neoplastic agents (including immunotherapy and investigational agents) within 3 weeks prior to the first dose of study treatment, or any residual AEs from prior anti-cancer therapies that have not resolved to Grade ≤1. Use of any investigational drugs within 3 weeks prior to the first dose of study treatment is also

prohibited. Note: COVID-19 vaccinations that are authorised but not approved should not be considered as investigational agents for the purposes of study eligibility assessment.

7. Patients with a known hypersensitivity to any RXC004 excipients.
8. Patients with a contra-indication for denosumab treatment including:
   - Known hypersensitivity to denosumab or any of the excipients
   - Severe untreated hypocalcaemia
   - Unhealed lesions from dental or oral surgery
9. Patients who are pregnant or breast-feeding
10. Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.
11. Known active HIV, hepatitis B (HBV), or hepatitis C (HCV) infections. Patients with a resolved HBV infection (defined as presence of hepatitis B core antibody [HBcAb] and absence of HBV surface antigen [HBsAg] or negative on polymerase chain reaction [PCR] for HBV DNA) are eligible. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
12. Use of any live or live-attenuated vaccines against infectious diseases (e.g., influenza nasal spray, varicella) within 4 weeks (28 days) of initiation of study treatment. Note: Patients that require COVID-19 vaccination within 4 weeks of initiation of study treatment should receive a non-live vaccine (e.g. one based on mRNA or fully inactivated/genetically modified viruses incapable of replication).
13. Mean resting corrected QTcF >470 ms, obtained from triplicate ECGs performed at screening.

There are no exclusion criteria specific to Modules 1 and 2. Module 3-specific exclusion criteria are listed below.

5.5 Module 3 Specific Exclusion Criteria

Participants are excluded from Module 3 (RXC004 + pembrolizumab) if any of the following criteria apply:

14. Patients with any contraindication to the use of pembrolizumab as per approved label (Summary of Product Characteristics or equivalent).
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137), and was discontinued from that treatment due to a Grade 3 or higher irAE.

16. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis. [Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system (CNS) disease.]
17. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of pembrolizumab in this study.
18. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
19. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
20. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
21. Has an active infection requiring systemic therapy.
22. Patients with a history of allogeneic tissue/solid organ transplant.
23. Patients with active infections, including tuberculosis, HIV, HBV, or HCV. Patients with a resolved HBV infection (defined as presence of hepatitis B core antibody [HBcAb] and absence of HBV surface antigen [HBsAg] or negative on PCR for HBV DNA) are eligible. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

5.6 Lifestyle Considerations

5.6.1 Contraception

1. Women must be 1 year post-menopausal, surgically sterile or agree to using enhanced contraceptive measures for the duration of the study, from the time of treatment initiation, and for 5 months after the last dose of study drug, with all male sexual partners. Highly effective methods of contraception must be used, which include having a vasectomised partner, sexual abstinence (defined as refraining from heterosexual intercourse during the study and for 5 months after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated by the Investigator, in relation to the duration of the study and the preferred/usual lifestyle of the patient), or one of the following: hormonal contraceptives which inhibit ovulation (oral, injectable, transdermal, intravaginal or implants), Intrauterine Device (IUD), Intrauterine Hormone-releasing System (IUS) (e.g., Mirena), or bilateral tubal occlusion.

2. Men must use a condom (with spermicide) during the study, and for 5 months after the last dose of study drug, with all sexual partners.
3. Men must not donate sperm for 5 months after the last dose of study drug.

5.6.2 Meals and Dietary Restrictions

Patients must fast (water to drink only) from at least 2 hours prior to taking a dose to at least 1-hour post-dose for all doses. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g. grapefruit juice or marmalade) during the study **(**e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15g) of Seville orange marmalade daily).

For participants in Module 3, no additional meal or dietary restrictions are required with regard to pembrolizumab study treatment, unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.

5.6.3 Concomitant Treatments

5.6.3.1 Prohibited and Restricted Medications (Modules 1, 2, and 3)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study intervention or vaccination may be required. The investigator is to discuss prohibited medication/vaccination with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor, and the participant.

The following concomitant medication is prohibited:

1. The use of any natural/herbal products or other 'folk remedies'.
2. No other chemotherapy, or other anticancer therapy, including radiation therapy (except local treatment to a symptomatic solitary lesion), immunotherapy, and hormonal therapy (contraception and hormone replacement therapy is acceptable), or other investigational product is permitted other than the study treatments.
3. The use of some CYP3A4 inhibitors and inducers should be restricted prior to first dose of study treatment and throughout the study treatment, as RXC004 is observed to be exclusively metabolised by CYP3A4. For a list of prohibited CYP3A4 inhibitors and inducers and details of restrictions prior to the first dose of study treatment, please refer to Appendix E.

4. Drugs that are immunosuppressive or may cause secondary osteoporosis should not be administered (e.g. corticosteroids, pioglitazone or rosiglitazone). The following exceptions are allowed:
    - Use of immunosuppressive medication for the management of colitis events (per Appendix K), or pembrolizumab-related AEs (please refer to Appendix L).
    - Steroids required for the management of RXC004- or pembrolizumab-related AEs should be tapered to prednisolone ≤ 10 mg/day equivalent, before re-starting study treatment.
    - Systemic glucocorticoids when used for the following purposes:
        - To modulate symptoms of an AE that is suspected to have an immunologic aetiology
        - For the prevention of emesis
        - To premedicate for IV contrast allergies
        - To treat chronic obstructive pulmonary disease (COPD) exacerbations (only short-term oral or IV use in doses > 10 mg/day prednisone equivalent)
        - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
    - Other glucocorticoids when used for the following purposes:
        - For topical use or ocular use
        - Intraarticular joint use
        - For inhalation in the management of asthma or COPD.
5. Live or live-attenuated virus and bacterial vaccines should not be administered, e.g. yellow fever, measles, influenza nasal spray, COVID-19, rubella, mumps, typhoid, mycobacterium *tuberculosis* (BCG), *Yersinia pestis* (EV) within 30 days of starting study treatment, whilst the patient is receiving study medication and for 30 days following discontinuation of study treatment. Killed vaccines are allowed. Patients who require COVID-19 vaccination whilst on study should receive a non-live vaccine (e.g. one based on mRNA or fully inactivated/genetically modified viruses incapable of replication). Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

5.6.3.2 COVID-19 Vaccinations

COVID-19 vaccination is permitted before or during study treatment, with the exception of live or live-attenuated vaccines and replication-competent vector vaccines, which are prohibited within 30 days of starting study treatment and while on study treatment.

As COVID-19 vaccines are often prioritised for cancer patients, vaccination prior to the first

dose of study treatment is advisable. Where possible, COVID-19 vaccinations should be given at least 72 hours before starting study treatment and study treatment should not commence until any acute adverse effects from vaccination have resolved to at least Grade 1. If this is not possible, investigators should follow their local prescribing information and policies when considering whether a patient on study treatment should receive a COVID-19 vaccination. If COVID-19 vaccination is given during the study (including the screening period), then please ensure that all the relevant information is recorded in the concomitant medication eCRF (i.e. vaccine name, manufacturer, date(s) given and dose).

5.6.4 Other Lifestyle Considerations

Patients taking RXC004 are advised to avoid exposure to direct sunlight and the use of tanning equipment.

5.7 Screen Failures

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

Individuals who do not meet the calcium and/or vitamin D3 laboratory criteria for participation in this study may be retested after starting calcium/vitamin D3 supplementation. Repeating laboratory tests within the screening period will not be considered as a rescreen.

5.8 Pre-Screening Genetic Testing for Module 1

For Module 1, all enrolled patients' tumours will be required to have a mutation in the RNF43 gene. Eligible patients will be identified by either a central genetics screening approach or local laboratory assessments.

Central Testing - UK

CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI

[redacted]

Data from central genetic screening will be shared with investigators to aid future treatment decisions.

[redacted]

Local Testing - UK

Patients with predicted loss of function RNF43 mutations from other local testing will also be eligible to enter the study, provided that the assay used for testing has adequate analytical validation for this purpose (i.e. fully [redacted] for the purpose of investigating RNF43 mutations; partially [redacted] for their analytical performance or having achieved a minimum validation specification of >90% for Analytical Sensitivity / PPA and >95% for Analytical Specificity / NPA for the detection of the aberrations in the genes of interest and performed in an ISO accredited, CLIA or CAP accredited lab). If patients have insufficient [redacted] as is often the case for patients with pancreatic cancer, an RNF43 mutation that has been detected in [redacted] by a commercial plasma testing panel will be accepted for enrolment, provided the test meets the validation specifications described above. If aberrations are detected by local tests that are not included in the list in Appendix F, these may be included in the study on discussion with the Sponsor, if they are predicted to lead to a loss of function in the RNF43 protein based on pre-determined criteria.
[redacted]

Central Testing – Australia

Potential participants for Module 1 will be identified via their participation in the MoST Framework Protocol screening programme (Australia New Zealand Clinical Trials Registry: ACTRN12616000908437). All pre-screening activities (listed below) will be conducted as part of the MoST Framework Protocol screening programme:

- Pre-screening informed consent

- CCI [redacted]
- Genetic screening for RNF43 mutations

CCI [redacted]

CCI [redacted]

If patients have insufficient CCI [redacted] as is often the case for patients with pancreatic cancer, an RNF43 mutation that has been detected in CCI [redacted] may be accepted for enrolment, subject to Sponsor notification.

For Module 2 and Module 3, potential subjects may be identified via their participation in the MoST Framework Protocol screening programme, or recruited from outside of the MoST Framework Protocol screening programme.

6 STUDY TREATMENT

6.1 Study Treatment(s) Administered

6.1.1 Investigational Products

Details for RXC004 and denosumab, which will be administered in all Modules, are provided in Table 10. Details for pembrolizumab, which will be administered in Module 3 only, are provided in Section 12.7.

Table 10 Investigational Products

Treatment	RXC004	Denosumab
Module	Module 1, 2 and 3	Module 1, 2 and 3
Type	Drug	Biologic
Dose Formulation	0.5mg or 1mg capsules	Ampule
Dosage Level(s)	• 1 mg QD (Cohort 2, Module 2) • 1.5 mg QD (Module 3) • 2 mg QD (Module 1, and Cohort 1, Module 2)	120 mg once every month
Route of Administration	Oral	SC injection
Use	Experimental	Prophylactic
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	RXC004 will be provided in white 50 mL HDPE Duma bottles. Each bottle will be labelled as required per country requirement	Study Intervention will be provided in a vial containing 120 mg in a 1.7 mL solution. Each vial will be labelled as required per country requirement

HDPE, high-density polyethylene; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; QD, once daily; SC, subcutaneous.

6.2 Preparation/Handling/Storage/Accountability of Study Treatments

Details for RXC004 and denosumab are provided below. For pembrolizumab (applicable to Module 3 only), see Section 12.7.2.

6.2.1 RXC004

RXC004 will be supplied by Redx as 0.5 mg and 1.0 mg capsules. A complete description of the chemistry and formulation may be found in the Investigational Medicinal Product Dossier. The Quality Control Standards and requirements for RXC004 study medication are described in separate release protocols/ Certificate of Analysis.

RXC004 is formulated as two dosage strengths capsules manufactured by Quay Pharma, Deeside Industrial Park, CH5 2NS, United Kingdom. The RXC004 capsules strengths are 0.5 mg and 1.0 mg for oral administration. Stability testing of RXC004 is ongoing. Please

refer to the current IMP label for the Expiry Date associated with the current shelf-life of the product.

Patients must fast (water to drink only) for at least 2 hours prior to taking a dose to at least 1 hour post-dose for all doses.

6.2.2 Denosumab

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity specifically to RANKL, preventing RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

Denosumab (XGEVA®) is approved administered at 120 mg SC once monthly for use in the prevention of skeletal-related events in patients with advanced cancers with bone metastases.

The use of denosumab in this trial is outside labelled use as patients may not have bone metastases. The rationale for its prophylactic use in all patients is as a bone-protection measure based on the increased risk of bone fragility with RXC004 treatment.

6.3 Study Treatment Compliance

The first dose of RXC004 will be taken at site under medical supervision. The date, and time of dose administered at site will be recorded in the source documents and recorded in the eCRF. When patients self-administer RXC004 at home, compliance with study treatment will be assessed at each visit. Compliance will be assessed by collection of a patient diary cards and counting of returned capsules, during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of RXC004 capsules dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

Details for pembrolizumab (Module 3) are provided in Section 12.7.3.

6.4 Reporting of Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

Concomitant medication may be given as medically indicated with the exception of prohibited concomitant medication (Section 5.6.3 and Appendix E).

The timeframe for reporting concomitant therapy is from Screening (within 28 days prior to first dose of study treatment) up to 30 days after last dose of RXC004, and up to 90 days after last dose of pembrolizumab in Module 3. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5 Dose Modification

Dose modifications and stopping criteria for RXC004 are detailed in Section 6.5.1.

For participants in Module 3 (RXC004 in combination with pembrolizumab): Dose modifications and stopping criteria for pembrolizumab are detailed in Appendix L. If either agent is interrupted or discontinued for a related AE, the other agent (pembrolizumab or RXC004) may be continued if the patient is judged (by the investigator) to be receiving clinical benefit.

6.5.1 Dose Modifications for RXC004

RXC004 dose reduction and interruption are permitted.

RXC004 may be dose interrupted (withheld) until a clinically significant (any grade) and/or a grade $\geq$ 3 related adverse event resolves to baseline or $\leq$ grade 2. RXC004 may also be withheld if it is necessary to give a concomitant medication that is a moderate or strong CYP3A4 inhibitor.

Colitis events may occur with RXC004 or with pembrolizumab, and should be managed per Appendix K and, for participants in Module 3, the dose modification and toxicity management guidelines for irAEs associated with pembrolizumab (Appendix L 1) if applicable. For patients receiving the combination treatment with RXC004 and pembrolizumab, the most conservative guideline should be followed.

RXC004 dose interruption and stopping criteria are detailed in Table 11.

Table 11 RXC004 Dose Modification and Stopping Criteria

Event	Action
Colitis events (e,g. Colitis, ileitis, enterocolitis etc)	
Grade 1	Reduce RXC004 to a lower dose (see Table 12 for dose reduction scheme) and manage per Appendix K. If receiving RXC004 in combination with pembrolizumab, no additional action is required for pembrolizumab.
Grade 2	Interrupt RXC004. Manage as per Appendix K. When event has resolved to Grade ≤ 1[a] and steroids have been tapered to prednisolone ≤ 10 mg per day (or equivalent), resume RXC004 at a lower dose (see Table 12 for dose-reduction scheme). If event recurs after re-starting study treatment, then RXC004 should be permanently discontinued. If receiving RXC004 in combination with pembrolizumab, interrupt pembrolizumab and see Appendix L for guidance.
Grade 3	Interrupt RXC004. Manage as per Appendix K. When event has resolved to Grade ≤ 1[a] and steroids have been tapered to ≤ 10 mg of prednisolone per day (or equivalent), resume RXC004 at a lower dose (see Table 12 for dose reduction scheme). If event recurs after re-starting study treatment, then RXC004 should be permanently discontinued. If receiving RXC004 in combination with pembrolizumab; **permanently discontinue both agents** and manage as per Appendix K and Appendix L.
Grade 4	If receiving RXC004, either as monotherapy or in combination with pembrolizumab: **Permanently discontinue both agents**. Manage per Appendix K and Appendix L.
Dysgeusia events	
Grade 1/2	RXC004 related: Manage per Appendix J Consider dose reduction, depending on clinical symptoms Interrupt RXC004 treatment if dysgeusia is associated with >5kg weight loss from baseline.

Table 11 RXC004 Dose Modification and Stopping Criteria

Event	Action
Grade 2 associated with a 10-20% decrease in body weight	RXC004 related: Manage per Appendix J Reduce RXC004 to a lower dose (see Table 12 for dose-reduction scheme).
Grade 2 associated with a > 20% decrease in body weight	RXC004 related: Permanently discontinue RXC004. If receiving RXC004 in combination with pembrolizumab, the pembrolizumab can continue if clinical benefit is judged by the Investigator.
Other AEs	
RXC004-related Grade 3 toxicity (1st event)	Interrupt RXC004 and provide supportive care, resume a lower dose level when resolved (≤ Grade 2 or returns to baseline). See Table 12 for dose-reduction scheme.
RXC004-related Grade 3 toxicity (subsequent repeat of a previously experienced event)	Permanently discontinue the related study treatment
Any Grade 4 toxicity	Permanently discontinue the study treatment.
All Grade events	Study treatment can be interrupted or discontinued for any clinically significant AEs that in the investigator's opinion warrants treatment interruption or discontinuation.
Bone events	
Confirmed (by imaging) RXC004-related fragility bone fracture (excluding grade 1 vertebral deformities)	Permanently discontinue RXC004. Pembrolizumab can continue if the patient is receiving clinical benefit as judged by the investigator.
Patients with a DEXA scan showing >7% worsening in BMD at lumbar spine or total hip compared to baseline	Permanently discontinue RXC004. Pembrolizumab can continue if the patient is receiving clinical benefit as judged by the investigator.
An individual increase in β-CTX of CCI from the baseline (screening) value or an individual measurement of CCI	Permanently discontinue RXC004 unless the patient has received clinical benefit (investigator assessment) and continued treatment is warranted. Pembrolizumab treatment can continue if the patient is receiving clinical benefit as judged by the investigator.
COVID-19 infection	
Positive COVID-19 test	Interrupt RXC004, until acute symptoms have resolved.

Table 11 RXC004 Dose Modification and Stopping Criteria

Event	Action
Major surgery	Interrupt RXC004, resume at full dose. Pembrolizumab does not need to be interrupted. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after RXC004 is swallowed, the dose may be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed RXC004 dose	Allowed to take the scheduled dose up to 4 hours after the scheduled dose time. If greater than 4 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.

[a] Attempts should be made to confirm that the colitis has resolved to Grade ≤ 1 (e.g. normalised CRP or fecal calprotectin if raised during event; GI appearance normalised on X-ray/CT or endoscopy) before restarting RXC004.

AE, adverse event; BMD, bone mineral density; COVID-19, Coronavirus disease 2019; QD, once daily.

Toxicity will be assessed using the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 5.0, unless otherwise specified. Every effort should be made to administer trial treatment at the planned dose and schedule. However, patients experiencing RXC004-related toxicities may have their RXC004 dose modified as outlined below.

RXC004 related toxicities observed during the course of the study will be managed by interruption of RXC004 and initiation of appropriate treatment as judged by the Investigator. Upon re-starting treatment the guidance for dose reduction in RXC004 contained in Table 12 should be followed.

Table 12 Guidance for Dose Reductions for RXC004-related Adverse Events

Dose Level	RXC004 (Module 1 and Module 2, Cohort 1 only)	RXC004 (Module 3 only)	RXC004 (Module 2, Cohort 2 only)
Initial dose level	2 mg QD	1.5 mg QD	1 mg QD
1st dose reduction • Grade 3 toxicity (1st event) • Grade 1/2 dysgeusia [a]	Hold RXC004[b]. Upon resolution to ≤ Grade 2, restart at 1.5 mg QD Dose reduce to 1.5 mg QD	Hold RXC004[b]. Upon resolution to ≤ Grade 2, restart at 1 mg QD Dose reduce to 1 mg QD	Hold RXC004[b]. Upon resolution to ≤ Grade 2, restart at 0.5 mg QD Dose reduce to 0.5 mg QD
2nd dose reduction • Grade 3 toxicity (1st unique event) • Grade 3 toxicity (recurrence of a previously experienced Grade 3 event) • Grade 2 dysgeusia associated with > 20% weight loss[a]	Hold RXC004[b]. Upon resolution to ≤ grade 2, restart at 1 mg QD Not permitted. Permanently discontinue RXC004 Not permitted. Permanently discontinue RXC004	Hold RXC004[b]. Upon resolution to ≤ Grade 2, restart at 0.5 mg QD Not permitted. Permanently discontinue RXC004 Not permitted. Permanently discontinue RXC004	Not permitted. Permanently discontinue RXC004.
3rd dose reduction	Not permitted. Permanently discontinue RXC004.	Not permitted. Permanently discontinue RXC004.	Not applicable

[a] Dependent on clinical symptoms, excluding other possible causes and despite optimal treatment.
[b] RXC004 can be resumed after an interruption, as long as no other treatment discontinuation criteria have been met. Patients who experience disease progression while RXC004 is held will not be eligible to be treated beyond progression.

QD, once daily.

6.6 Access to Study Treatment after the End of the Study

Any patients still receiving investigational product at the time of the data cut off will be able to continue to receive investigational products within the current study while in the Investigator's opinion, deriving clinical benefits and not fulfilling the discontinuation criteria.

In Module 3, for those patients who are continuing on combination therapy with RXC004 and pembrolizumab, both agents can be administered until discontinuation criteria are met. Patients who discontinue RXC004 may continue to receive pembrolizumab q6w alone. The continued access to pembrolizumab will end when a criterion for discontinuation is met or 18 doses of pembrolizumab (q6w dosing) have been administered (approximately 2 years), whichever is sooner.

Assessments will revert to standard of care for each individual site.

In Modules 1 and 2, patients will continue to be monitored for all SAEs up to 30 (+3) days after the last dose of RXC004 (i.e. patients treated with RXC004 monotherapy only).

In Module 3, patients will continue to be monitored for all AEs and Events of Clinical Interest for pembrolizumab up to 30 (+3) days after the last dose of RXC004 or pembrolizumab. Follow-up for SAEs will continue for 30 (+3) days after the last dose of RXC004 and for 90 days after the last dose of pembrolizumab.

A paper form process will be used for AE, Events of Clinical Interest, and SAE reporting. All SAEs and overdoses will be reported until 30 days after last dose of RXC004 (Modules 1 and 2) or 90 days after the last dose of pembrolizumab (Module 3). All pregnancies will be reported up to 5 months after the last dose of the study drug(s).

The investigational product will be supplied to sites manually. The investigational product dispensation and reconciliation will be handled by the study team at each patient's visit. The investigational product accountability information must still be collected until all patients have completed treatment.

7 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

An individual patient will not receive any further IP if any of the following occur:

- Patient decision to withdraw from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment.
- Clinical or RECIST 1.1-defined radiological progression. (Symptomatically/clinically

stable patients may continue treatment until symptomatic/clinical progression or second RECIST 1.1 progression [relative to the first 'on study treatment' RECIST 1.1 progression]). See Section 7.1.1 for details for continuing study treatment after RECIST1.1 defined progression.

- An AE that meets RXC004 discontinuation criteria in Table 11.
- Pregnancy or intent to become pregnant.
- Initiation of alternative anticancer therapy including another investigational agent .
- Non-compliance with the study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal from treatment with IP.

For participants in Module 3 (RXC004 in combination with pembrolizumab), the following additional criteria for discontinuation of pembrolizumab apply:

- Completion of 18 administrations (approximately 2 years) with pembrolizumab (q6w dosing). [Note: The number of administrations is calculated starting with the first dose of pembrolizumab.]
- Any study intervention-related toxicity specified as a reason for permanent discontinuation of pembrolizumab as defined in the guidelines for dose modification due to AEs in Appendix L.
- Discontinuation of treatment may also be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

Discontinuation from study treatment is NOT the same thing as a withdrawal from the study. If study treatment is permanently discontinued, the participant will remain in the study to be evaluated for safety, progression (if the patient discontinues for a reason other than progression) and survival. See the Schedule of Assessments (Table 15, Table 16, and Table 18) for data to be collected at the time of discontinuation of study treatment and during follow-up.

7.1.1 Treatment of Symptomatically Stable Patients after RECIST 1.1 Defined Progression

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

Patients who wish to continue study treatment after RECIST1.1-defined progression should be informed of all other alternative treatment options available to them by the treating physician and sign an additional consent that they wish to continue study treatment. A decision to continue study treatment after initial progression must also be discussed and agreed by the treating physician and the Sponsor.

The criteria for continuing treatment after initial RECIST 1.1-defined progression are as follows:

- Signed patient consent for treatment after progression.
- The patient does not have any significant, unacceptable, or irreversible toxicities indicating that continuing treatment will not further harm the patient.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in ECOG performance status >1.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g. CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
- Study treatment was not on hold/interrupted at time of progression.

Patients continuing study treatment after initial RECIST 1.1-defined progression should continue RECIST scans per the Schedule of Assessments (the next tumour assessment should be at least 4 weeks after the first RECIST 1.1-defined progression and no later than the next regularly scheduled imaging timepoint).

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified options to continue collecting safety and efficacy information (e.g., telephone contact, a contact with a relative or treating physician, or collecting information from medical records).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be

carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 15, Table 16, and Table 18). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within 28 days of the first dose of study treatment.

- The maximum amount of blood collected from each participant over the duration of the study will not exceed 500 mL.

8.1 Efficacy Assessments

The following efficacy assessments will be conducted for each patient in this study – PFS, objective response (CR, PR, SD or PD), CCI [redacted], % change in the sum of target lesions and OS. The primary and secondary endpoints for each module are specified in Section 3.

Efficacy assessments other than OS will be derived using investigator RECIST 1.1 assessments.

8.1.1 Tumour Assessments

Tumour assessments use images from CT or MRI, collected during screening/baseline and at regular (follow-up) intervals during the study. The same imaging method should be used throughout the study. It is important to follow the tumour assessment schedule as per the SoA. Tumour assessments will continue until RECIST1.1-defined radiological progression. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

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

In addition, if available, the last 2 imaging scans taken prior to the screening scan for this study and/or their reports should be kept for possible central/sponsor review.

8.1.2 Survival Assessments

Assessments for survival must be made following treatment discontinuation, as indicated in the SoA. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected. In addition, patients on treatment or in survival follow-up will be contacted within 7 days of the DCO for any survival analyses to provide complete survival data.

8.2 Safety Assessments

8.2.1 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the SoA. 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 appropriate 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.

The following laboratory variables will be measured (Table 13).

Table 13 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
All modules of the study:	
Haemoglobin (Hb)	Creatinine and creatinine clearance[a]
Total white-cell count	Bilirubin, total
Neutrophils (absolute count or %)	Alkaline phosphatase (ALP)
Platelet count	Aspartate transaminase (AST)
Lymphocytes (absolute count or %)	Alanine transaminase (ALT)
Coagulation (INR APTT)	Albumin
	Potassium
	Phosphate
	Urea
	Calcium, total and corrected
Other tests: [c]	Magnesium
HIV antibodies	Sodium
Hepatitis B surface antigen	Glucose (random)
Hepatitis C antibodies	Lipase
	LDH
	Amylase
	CRP
	Vitamin D [b]
Module 3 only:	
	TSH
	Triiodothyronine (T3) or free T3
	Free thyroxine (T4)

[a] Creatinine clearance at baseline only.
[b] Required at baseline/screening only.
[c] These tests are mandatory for Module 3.

APTT, activated partial thromboplastin time; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

8.2.2 Physical Examinations

A physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen); otherwise, symptom-directed.

Physical examinations will be performed at timelines as specified in the SoA (Table 15, Table 16, and Table 18).

8.2.3 Vital Signs

The following vital signs will be performed at timelines as specified in the SoA (Table 15 Table 16, and Table 18):

- Blood pressure
- Pulse rate
- Temperature
- Respiration rate
- O_2 saturation (as clinically indicated)
- Weight
- Height (recorded at baseline only)

8.2.4 Electrocardiograms

Triplicate ECG will be performed at timepoints as specified in the SoA. 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).

All ECG traces should be kept by site for possible central/Sponsor review.

At selected sites, digital ECG collection may take place using ambulatory Holter monitoring equipment on Cycle 0 Day 1 and Cycle 1 Day 15. The information will be stored and analysed centrally.

8.2.5 Performance Status

8.2.5.1 Karnofsky Performance Status

Karnofsky performance status will be assessed for patients in Module 1 (PDAC) at the times specified in the Module 1 schedule of assessments (see Appendix G).

8.2.5.2 ECOG Performance Status

ECOG performance status will be assessed for patients in Module 2 (BTC) at the times specified in the Module 2 and Module 3 and Module 3 SoAs (See Appendix G).

8.2.6 Other Safety Assessments

Pregnancy tests

All women of child-bearing potential will have pregnancy tests (urine or serum) performed at timepoints as specified in the SoA (Table 15, Table 16, and Table 18).

Screening safety tests

In Module 3, tests for HIV antibodies, hepatitis B surface antigen, and hepatitis C antibodies will be performed for all patients treated with RXC004 and pembrolizumab combination at screening (Table 18).

8.3 Adverse Events and Serious Adverse Events

The Principal investigator (PI) is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

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

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events (and Events of Clinical Interest for pembrolizumab) will be collected from time of signature of main study informed consent form throughout the treatment period and until the 30 days after last dose of RXC004 (for patients treated with RXC004 monotherapy) or 90 days after the last dose of pembrolizumab (for patients treated with RXC004 and pembrolizumab combination therapy), or 30 days following cessation of pembrolizumab treatment if the participant initiates new anticancer therapy, whichever is earlier.

SAEs will be recorded from the time of signing of main study informed consent form.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at 90 days after last dose of IP should be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. Redx retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade changes
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- Outcome
- Whether treatment was required

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Serious criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question: ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated, laboratory values, vital signs, bone turnover biomarkers and DEXA scans should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not be limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g. dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

If a patient demonstrates an AST or ALT ≥3x ULN together with total bilirubin ≥2x ULN, it must be reported to the Sponsor and/or designated CRO within 24 hours, in the absence of known alternative aetiology. Prompt reporting of cases meeting Hy's Law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The Investigator is responsible for immediately determining whether a patient meets potential Hy's Law criteria. The Investigator needs to perform additional examinations for this and confirm the results with the medical monitor.

8.3.7 Disease Progression

Disease progression can be 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 to 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.

8.3.7.1 Management of Biliary Tract Obstruction

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures should be undertaken to diagnose (e.g. by ultrasound and/or CT scan) and relieve the obstruction (e.g. by ERCP/PTC +/- stent insertion/drainage). Treatment will be delayed until the LFTs have improved to pre-obstruction levels.

Biliary tract obstruction by itself shall not constitute evidence of disease progression. CT or MRI/MRCP imaging will be performed at the planned time points; however, if there is radiological evidence of objective disease progression during the investigation of obstructive jaundice, treatment with RXC004 shall be discontinued.

8.3.8 Disease-Under Study

Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform the appropriate Sponsor representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all the necessary information is provided to Patient Safety **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. investigators or other site personnel must inform the Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

The reference document for definition of expectedness of RXC004 is the RXC004 IB, and the IB for pembrolizumab.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to Sponsor representative except for if the pregnancy is discovered before the study participant has received any study drug.

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, investigational product should be discontinued immediately.

The Sponsor or Sponsor designated Safety Services must be notified within 24 hours of the initial report and any follow-up reports of a female patient or a male patient's female partner becoming pregnant during the course of the study and for 5 months after the last dose of the study drug(s) via the Pregnancy Report Form. Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication or a female patient or male patient's female partner experiences signs or symptoms of pregnancy complications; congenital abnormalities/birth defects and spontaneous miscarriages should be reported as SAEs. The contact information for pregnancy reporting is the same as for SAE reporting. Female patient(s) who become pregnant will be followed at least monthly until the outcome of the pregnancy is known. In order for the Sponsor or designee to collect pregnancy surveillance information, the pregnant patient or partner must sign an ICF. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for at least 5 months following the last dose.

Pregnancy of the participant's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 5months after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 COVID-19 Infections

COVID-19 infections occurring from time of signature of the main study ICF until 30 days after discontinuation of study treatment should be reported as adverse events. Patients who test positive for COVID-19, but do not have any symptoms should be reported as 'asymptomatic COVID-19'. If COVID-19 is suspected but not confirmed by a diagnostic test,

then ‘suspected COVID-19’ should be reported. The AE term for the ‘suspected COVID-19’ should be updated when the results of the diagnostic test are known to reflect the confirmed COVID-19 or alternative diagnosis (e.g. common cold, influenza etc).

8.3.12 Dysgeusia

Loss of taste (dysgeusia) is an on-target adverse event known to occur with porcupine inhibition. According to CTCAEv5, there are only two grades of dysgeusia:

Grade 1 - Altered taste but no change in diet.

Grade 2 - Altered taste with change in diet (e.g. oral supplements); noxious or unpleasant taste; loss of taste.

As dysgeusia is poorly characterised by CTCAE grade alone, site research personnel will complete a taste assessment (consisting of a specific set of questions and an oral examination) at screening for each patient enrolled, and for any patient who reports dysgeusia in response to the open question from the study site staff: ‘Have you had any health problems since the previous visit/you were last asked?’. In such cases, the assessment will be performed at each visit until the adverse event has resolved. The information will be recorded and analysed as part of the overall safety objective of the study.

8.3.13 AEs of Potential Interest (AEPI)

As discussed in Section 2.3.1, colitis events and bone toxicity events are classified as AEPIs for RXC004. This means that additional information will be captured on the CRF for any CTCAE-preferred terms that fall into these categories. These terms will be defined in the CRF Guidelines and reviewed at any update of the CTCAE definitions.

Events of Clinical Interest for pembrolizumab are described in Section 12.10.

8.4 Overdose

For this study, any dose of RXC004 greater than the daily assigned dose will be considered an overdose.

Investigators should be advised that any patient who receives an overdose should be monitored closely, managed with appropriate supportive care and followed up expectantly. There are no data regarding RXC004 overdose in humans. An overdose and AEs should be treated per standard medical practice.

Dosing details should be captured in the eCRF. If the patient receives a dose of a study drug that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as AEs in the eCRF and, if serious, submitted to the Sponsor’s

designated safety contact on an SAE Report Form. Do not record the overdose as an AE if the patient is not symptomatic.

For this study (Module 3), an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
- Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

8.5.1 Pharmacokinetics

Venous blood samples (2 mL) for determination of concentrations of RXC004 in plasma, this may also permit investigation of any significant metabolites. Samples will be taken after a single dose of RXC004 in Cycle 0 Day 1 at designated times (Table 15, Table 16, and Table 18) up to 48 h post-dose and again at Cycle 1 Day 15 at designated times up to 24 h post-dose. Cycle 0 may be 3-7 days in duration to allow for flexibility in scheduling the full PK time course at Cycle 1 Day 15 to avoid weekend sampling if required. CCI [redacted] CCI [redacted] if required. The date and time that the last dose of RXC004 was administered prior to Cycle 1 Day 15 and the date and time of collection of each sample will be recorded.

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total number of samples and the total volume of blood taken from each patient will not exceed that outlined in the Lab Manual.

If a patient misses any doses of RXC004 within 3 days of PK sampling, please contact the Sponsor representative as to any effect on the changes required on the timing of the PK assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as per study plan, relative to baseline assessments.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of RXC004 concentrations in plasma will be analysed using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed.

In addition, the pharmacokinetic samples may be subjected to further analyses in order to investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

PK parameters will be estimated for each patient using WinNonlin® (Phoenix 64 V8 or higher) or suitable alternative. The following parameters will be derived, where appropriate, from the individual plasma-concentration-versus-time profiles of RXC004.

Where appropriate the following RXC004 plasma pharmacokinetic parameters will be estimated. These include:

Single dose:	
• **C_{max}**	Maximum observed plasma concentration
• **t_{max}**	Time to C_{max}
• **C_{min}**	Minimum observed concentration across the dosing interval
• **λz**	Terminal rate constant
• **$t_{½}$**	Terminal half-life
• **AUC_{0-24}**	Area under the plasma concentration-time curve from zero to 24 hours
• **AUC_{0-t}**	Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration
• **$AUC_{0-\infty}$**	Area under the plasma concentration-time curve from zero to infinity
• **AUC_{τ}**	Area under the plasma concentration-time curve across the dosing interval
• **CL/F**	Total plasma clearance after oral administration
• **Vz/F**	Apparent volume of distribution after oral administration

• **MRT**	Mean residence time
• **R_{ac}**	Accumulation ratio based on AUC_{τ} and C_{min} after the first and the last dose
• **Swing**	$(C_{max}-C_{min})/C_{min}$

Dose proportionality of exposure parameters will be explored. In addition to dose normalisation of Cmax and AUC values.

Additional PK parameters may be calculated as appropriate.

8.5.2 Pharmacodynamics

8.5.2.1 Collection of Samples

CCI [redacted]
CCI [redacted]

CCI [redacted]
CCI [redacted]
CCI [redacted]

CCI [redacted]
CCI [redacted]

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the patient consents to participate in the mandatory research components of the study.

Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA. CCI [redacted]
CCI [redacted]
CCI [redacted]

Details for collection, volumes, storage, and shipment of biologic samples will be detailed in a separate Laboratory Manual.

8.6.1.1 CCI [redacted]

Module 1 Centralised Pre-Screening in the UK

CCI [redacted] from UK patients will be sent to CCI [redacted]
CCI [redacted], during the centralised pre-screening phase in Module 1. This analysis is required to investigate the presence of RNF43 mutants required to be eligible for Module 1 of the study (see

Appendix F). Analysis will occur before enrolment, and data will be shared with investigators and patients, to aid future treatment decisions.

CCI will also be screened from the CCI These data will be used to retrospectively investigate whether CCI CCI

CCI performed by CCI CCI CCI

Module 1 Local Testing - UK

PDAC patients with prior documented RNF43 LoF mutations (per Appendix F) will also be eligible for Module 1 of the study provided that the panel used is fully CCI CCI CCI If patients are enrolled in the study based on local laboratory assessments, then an optional archival CCI CCI will be collected at screening and sent for central genetic screening as described in Section 5.8. If an archival CCI is not available or not consented to, then a sample of the study baseline CCI may be sent for the central genetic screening.

Module 1 Centralised Pre-Screening in Australia

In Australia, patients with eligible RNF43 LoF mutations detected in archival FFPE tumour samples (see Appendix F) will be identified via their participation in the MoST Framework Protocol screening programme (Australia New Zealand Clinical Trials Registry: ACTRN12616000908437). CCI CCI If an CCI CCI is not available or not consented to, then a sample of the study CCI CCI CCI may be used for this purpose.

Module 2 and Module 3 Genetic Analysis

An CCI (mandatory, if available) will be collected at screening from patients enrolled in Module 2 and Module 3, for CCI if there is a CCI of CCI that may CCI This research will involve analysis of CCI

8.6.1.2 Exploratory Biomarkers

CCI

The study mandates that CCI are collected at baseline and 'on treatment' at time points specified in the SoA, as long as it is technically feasible and safe to do so. CCI CCI that may be assessed include (but are not limited to), CCI CCI CCI. The CCI of these CCI may be correlated to clinical response.

CCI

CCI may be prepared from whole blood samples obtained from patients at timepoints specified in the SoA. Quantification of CCI and/or CCI CCI Analysis may include (but is not limited to), the CCI of CCI Correlations with outcome data may be performed on CCI with the aim of identifying useful CCI thresholds for identifying patients likely to receive benefit.

CCI

Blood samples for analysis of CCI will be obtained from all patients as specified in the SoA. Overall CCI and/or CCI in CCI may be assessed using CCI Such measurements may be correlated with response.

CCI

Blood sample for analysis of CCI will be obtained from patients at timepoints specified in the SoA. The concentrations of a panel of relevant CCI, CCI CCI. Such measurements may be correlated with response.

CCI

CCI will be taken from a subset of patients recruited by sites within close proximity to Redx Pharma. CCI CCI will be used for analysis of CCI using CCI Such measurements may be correlated with response.

CCI

CCI frequently increased in CCI. Blood samples for CCI ill be obtained from patients at timepoints specified in the SoA and analysed locally. CCI may be correlated with response.

8.6.2 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.6.3 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.7 Health Economics

Not applicable in this study

9 STATISTICAL CONSIDERATIONS

The module specific statistical considerations can be found in Section 10.9 (PDAC) and Section 11.9 (BTC - monotherapy) and Section 12.11 (BTC – combination therapy).

9.1 Statistical Hypotheses

The statistical hypotheses for testing the activity of RXC004 in Module 1 (pancreatic cancer), and Modules 2 and 3 (biliary tract cancer) independently are:

$H_0 : p \leq p_0$

$H_1 : p \geq p_1$

Where H_0 is the null hypothesis, p is the observed response rate, p_0 is the response rate for available treatment options – CCI, H_1 is the alternative hypothesis and p_1 is the target response rate – CCI.

The primary summary measure for Module 1 and Module 2 is the progression free survival rate at 6 months. For module 1 the corresponding p_0 and p_1 are CCI% and CCI%. For Module 2 the corresponding p_0 and p_1 are CCI% and CCI%. The primary summary measure for Module 3 is the objective response rate. For Module 3 the corresponding p_0 and p_1 are CCI% and CCI%.

9.2 Sample Size Determination

The sample size determination for each module can be found in the module-specific statistical considerations - Section 10.9.1 for Module 1 (PDAC), Section 11.9.1 for Module 2 (BTC - monotherapy), and Section 12.11.1 for Module 3 (BTC – combination therapy).

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Population/Analysis set	Description
Full analysis set / Safety	All patients who enrolled and received at least one dose of RXC004 in Modules 1 and 2, and at least one dose of RXC004 or pembrolizumab in Module 3.
CCI	CCI CCI CCI

Population/Analysis set	Description
	CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]
PK analysis set	All patients in the safety analysis set who have had at least one blood sample.

9.4 Statistical Analyses

The statistical analysis plan will be finalised prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

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 in Modules 1 and 2, or 90 days after the last dose of pembrolizumab for the last subject in Module 3), or at the End of Study, whichever comes first. Depending on recruitment the data may be reported separately for each module. If reported together in one CSR the efficacy data will be presented separately for each module and not pooled. Baseline characteristics and safety data will be presented separately and selected data may be pooled, which will be detailed in the SAP.

All analyses, summaries and listings will be performed using SAS software (version 9.3 or higher). For categorical variables the frequency and percentage will be presented. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values will be presented. Missing data will not be imputed unless otherwise stated.

A baseline assessment will be defined as the last assessment performed prior to the first dose of study treatment. 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.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

Modules 1 and 2:

The primary endpoint is the progression free survival rate at 6 months, based on investigator

RECIST 1.1 assessments.

Progression free survival rate at 6 months is defined as the proportion of patients who remain alive and free of progression at 6 months.

Module 3:

ORR, defined as the proportion of patients with a best overall response of CR or PR, based on local investigator assessment, as defined in RECIST 1.1.

9.4.2.2 Secondary Endpoint(s)

Objective response rate is defined as the proportion of patients with a best overall response of CR or PR, based on local investigator assessment, as defined in RECIST 1.1. Confirmation of response is required for declaring PR or CR as the BOR. A confirmed response is defined as a CR or PR followed by a CR or PR a least 4 weeks later. The ORR will be summarised with accompanying 90% confidence interval calculated using the Clopper Pearson method. This will be calculated on the full analysis set and the evaluable analysis set. In the summary tables the incidence of unconfirmed responses will be presented as well as the patients with confirmed responses.

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of either CR, PR or stable disease (SD) for at least 6 weeks (corresponding to SD for at least 1 scheduled scan post baseline). A time window of 1 week around the visit will be applied. The DCR and associated 90% confidence interval, calculated using the Clopper Pearson method will be presented. This will be calculated on the full analysis set and the evaluable analysis set.

Progression free survival is defined as the time from first dose of study treatment until the date of disease progression or death (by any cause in the absence of progression), regardless whether the patient withdraws from the assigned study treatment or receives another anticancer prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of RECIST v1.1 assessment of their last evaluable scan; however, if the patient progresses or dies after 2 or more missed scheduled scanning visits, 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 unless they die due to progression within 2 scan visits of baseline. Progression free survival will be listed by patient and will be presented graphically using Kaplan-Meier plots. Median PFS, together with 3 month, 6 month and 12 months PFS rates will be estimated. The estimate for PFS rate at 6 months is the primary endpoint as detailed in Section 9.4.2.1.

Percentage change in tumour size will be derived at each visit by the percentage change from baseline in the sum of diameters of target lesions. The best percentage change in tumour size

will be the patient's value representing the largest decrease (or smallest increase) from baseline in tumour size. Best percentage change in tumour size will be presented in waterfall plots and percentage change in tumour size at each visit will be presented in a spider plot.

CCI

Overall survival is defined as the time from first day of study treatment 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 subject was known to be alive. Overall survival will be listed by patient and presented graphically using Kaplan-Meier plots. Median, 6 month and 12 month OS rates will be estimated.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

CCI

9.4.3 Safety

9.4.3.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset after dosing and pre-existing AEs that worsen after the start of dosing and within 30 days of stopping RXC004 monotherapy, or 90 days after the last dose of pembrolizumab (for patients in Module 3), or 30 days following cessation of pembrolizumab study treatment if the patient initiates new anticancer therapy, whichever is earlier. For AEs, verbatim terms in the CRF will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory activities (version 22.0 or later). CTCAE criteria v5.0 will be used to grade the severity of AEs. The incidence of TEAEs will be summarised by preferred term and system organ class as well as severity. Treatment-related TEAEs will be summarised in the same way. Per-patient incidence of SAEs will also be produced.

By patient, listings of all AEs, deaths, SAEs and TEAEs leading to discontinuation will also be produced.

9.4.3.2 Laboratory Parameters

Shift tables to characterise changes from baseline to on treatment will be presented for haematology, clinical chemistry and coagulation parameters. Laboratory tests with numerical grading criteria in the NCI CTCAE v5.0 will be graded accordingly. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE v5.0, results will be classified as low, normal or high based on laboratory normal ranges,

9.4.3.3 Vital Signs

Vital signs data will be presented in listings. Abnormal vital signs values will be identified as those outside (above or below) the reference range. Vital signs data will be summarised using descriptive statistics.

9.4.4 Other Analyses

9.4.4.1 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarised. For continuous demographic variables, results will be summarised and presented as n, mean, standard deviations, median and minimum and maximum values. For categorical variables the frequency and percentage of patient will be used.

9.4.4.2 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to standard names using the World Health Organization Drug Dictionary and further coded to the appropriate Anatomical-Therapeutic-Chemical code.

Prior medications will be defined as medications that stopped before the first dose of study drug and will be summarised and listed.

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug or (2) started on or after the date of the first dose of study drug. Concomitant medications will be summarised and listed.

9.5 Interim Analyses

There are no formal interim analyses planned.

9.6 Safety Monitoring Committee

An SMC will be appointed to review safety data from patients in this study and a second study of RXC004 in patients with colorectal cancer (RXC004/0002).

The SMC will comprise experts in the disease areas under investigation, who may be study investigators, a biostatistician and an independent bone metabolism expert. The SMC will be convened to review the safety and tolerability of RXC004 at regular intervals.

The safety reviews will start when approximately [redacted] patients across the phase 2 clinical trial program have been dosed for at least 1 cycle of study treatment and will continue every 6 months until the phase 2 studies close or last patient discontinues study treatment (whichever occurs first). A safety review of the combination data will be conducted after [redacted] patients have received the combination of RXC004 and pembrolizumab for at least 1 cycle. Additional safety reviews may be performed at other times as deemed appropriate by the Sponsor or SMC.

As 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.

MODULE 1 (PDAC)

10 MODULE 1 (PDAC)

10.1 Background

In 2020, it is estimated that pancreatic cancer will account for 18% of all newly diagnosed cancers in the US (Siegel et al 2020). For metastatic pancreatic cancer, which accounts for approximately 50% of pancreatic cancer diagnoses, the prognosis remains poor with a median OS of 10-12 months with SoC therapy (Thibodeau and Voutsadakis 2018, Von Hoff et al 2011, Conroy et al 2011 and Burris et al 1997). Standard first-line therapies for metastatic pancreatic cancer are FOLFIRINOX (patients with performance status 0-1) or gemcitabine (GEM) combinations, such as GEM plus Nab-paclitaxel (PS 0-2) or GEM plus cisplatin (for patients with BRCA mutations).

There is no standard second-line treatment; therapy option depends on previous treatment and performance status, and include combination or single agent chemotherapies, targeted agents and chemoradiation. Second-line studies have reported PFS of 1.5-3 months and OS of 3-7 months (Wang-Gillam et al 2016, Pelzer et al 2011 and Citterio et al 2018).

10.2 Module 1 Rationale

RXC004 is a small-molecule PORCN inhibitor which reduces Wnt signalling and therefore may offer an opportunity to deliver clinical benefit in tumours that have aberrantly activated Wnt signalling.

RNF43 is an integral membrane E3 ubiquitin ligase that promotes degradation of cell-surface Wnt receptors. Approximately 5-10% of all pancreatic cancers harbour a LoF RNF43 mutation (Waddell et al 2015, Jiang et al 2013, Bailey et al 2016), which leads to increased Wnt receptors at the cell surface and hence hyper-activated Wnt signalling.

Blocking Wnt signalling with PORCN inhibitors has been shown to suppress the growth of RNF43-mutant pancreatic cancers in pre-clinical models (Madan et al 2016, Jiang et al 2013). Furthermore, RXC004 has shown activity in pre-clinical CAPAN 2 xenograft models, which carry a RNF43 LoF mutation.

RXC004 warrants further development in patients with RNF43-mutation positive advanced (unresectable)/metastatic PDAC that has progressed following first-line standard of care treatment.

10.3 Benefit-Risk Assessment

10.3.1 RXC004 Risks

The risk assessment for RXC004 monotherapy treatment can be found in Section 2.3.

10.3.2 Benefit Assessment

This Module will evaluate RXC004 monotherapy in patients with advanced (unresectable)/metastatic pancreatic ductal adenocarcinoma with RNF43 loss of function (RNF43 LoF) who have received 1 prior systemic treatment.

In 2020, it is estimated that pancreatic cancer will account for 18% of all newly diagnosed cancers in the US (Siegel et al 2020). Approved first-line therapies for metastatic pancreatic cancer include FOLFIRINOX (a combination of irinotecan, folinic acid and fluorouracil) in patients with ECOG performance status 0-1 or gemcitabine (GEM) combinations, such as GEM plus Nab-paclitaxel or GEM plus cisplatin (for patients with BRCA mutations) in patients with ECOG 0-2 performance status. In patients with poorer performance status (ECOG 2) gemcitabine monotherapy is commonly used. For metastatic pancreatic cancer, which accounts for approximately 50% of pancreatic cancer diagnoses, the prognosis remains poor with a median OS of 7-12 months, an ORR of 7-32%, and median PFS of 3.7-6.4 months with 1st-line SoC therapy (Von Hoff et al 2011, Conroy et al 2011). Liposomal irinotecan combined with 5-FU/LV is the only approved treatment for 2nd-line metastatic PDAC (Wang-Gillam et al 2016) with ORR, mPFS and mOS of 16%, 3.1 and 6.2 months, respectively. The 6-month PFS rate (%) reported was CCI%. Second-line treatments have led to PFS of 1.5 to 3 months and OS of 3-7 months (Pelzer et al 2011, Wang-Gillam et al 2016, Citterio et al 2018).

The Phase 1 study of RXC004 enrolled unselected patients with advanced cancers with a median of three prior lines of treatment. Of 18 RECIST-evaluable patients, five had SD, in one case lasting for up to 26 weeks. All five of these patients with SD had Wnt-ligand-dependent tumours, supporting the hypothesis that RXC004 will have clinical activity in selected tumours that are dependent on Wnt ligand signalling pathways (Cook et al 2021).

In the expansion cohort of the WNT 974 study (Rodon et al 2021), stable disease was observed in 10 out of 28 patients, which was enriched in patients with RNF43 mutations.

RXC004 as a single agent therefore has potential to demonstrate clinical benefit in this in this genetically selected advanced (unresectable)/metastatic PDAC population with a large unmet medical need.

10.4 Objectives and endpoints

The objectives and endpoints for Module 1 can be found in Section 3.

10.5 Module 1 Study Design

Module 1 is an open label, multicentre module to evaluate the preliminary efficacy and safety of RXC004 monotherapy in RNF43 LoF mutation positive, advanced (unresectable)/metastatic PDAC, that has progressed following one prior systemic approved standard of care treatment for advanced (unresectable)/metastatic PDAC.

Patients will only be eligible for Module 1 if they have a documented RNF43 LoF mutation from either the centralised pre-screening activities or from a recognised panel in agreement with sponsor (see Appendix F and Section 5.8 for more details). CCI [redacted]

CCI evaluable patients will be enrolled in this module (see Table 14 for definition of evaluable patients).

The primary objective of the module is to assess the preliminary efficacy of RXC004 in terms of PFS rate (%) 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 until radiological disease progression (as defined by RECIST1.1). Following radiological progression, patients will be followed-up for safety and survival.

The rationale for the study design and endpoints can be found in Section 4. The general study design is summarised in Figure 1.

10.5.1 Rationale for Primary Endpoint

The current approved standard of care treatment for 2nd-line metastatic PDAC is liposomal irinotecan in combination with leucovorin/5-FU. A Phase 3 trial (NAPOLI-1 trial, Wang-Gillam et al 2016) evaluating this regimen reported a PFS rate at 6-months of CCI% with an ORR of 16%. Progression Free Survival (PFS) rate at 6-months is more appropriate (e.g. compared to Objective Response Rate (ORR)) to assess the anti-tumour effect of RXC004 as preclinical data indicate that RXC004 monotherapy used in a direct tumour targeting approach in patients with RNF43 LoF advanced (unresectable)/metastatic PDAC may deliver clinical benefit by a predominantly cytostatic rather than cytotoxic mechanism.

10.5.2 Rationale for Secondary Endpoints

ORR, DCR, PFS, OS and % change in target lesions are appropriate endpoints in an advanced (unresectable)/metastatic PDAC patient population and have been widely used and reported in clinical trials in this population.

10.6 Module 1 Patient Population

Module 1 will recruit male or female patients aged 18 years or older with histologically documented advanced (unresectable)/metastatic PDAC, with a documented RNF43 LoF mutation, that has progressed after one prior approved standard of care treatment for advanced (unresectable)/metastatic PDAC, a Karnofsky performance status ≥70 and a minimum life expectancy of 12 weeks.

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

10.6.1 Inclusion Criteria

Core- and Module 1 -specific inclusion criteria can be found in Sections 5.1 and 5.2, respectively. Participants are eligible to be included in the study only if all of the core- and Module 1-specific following criteria are met.

10.6.2 Exclusion Criteria

Core exclusion criteria can be found in Section 5.4. There are no Module 1-specific exclusion criteria. Participants are excluded from the study if any of the core exclusion criteria are met.

10.6.3 Lifestyle Considerations

Lifestyle considerations can be found in Section 5.6.

10.7 Study Treatment

Details of RXC004 monotherapy treatment can be found in Section 6. Discontinuation criteria for RXC004 can be found in Section 7.

10.8 Study Assessments

General details of the study assessment and procedures can be found in Section 8.

10.8.1 Schedule of Assessments

Table 15 Module 1 (PDAC) Schedule of Assessments

	Module 1 (PDAC)– Schedule of assessments								
	Pre-Screening[t]	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycle)**	**IP Discontinuation**	**30 day follow-up**	**Survival follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
Pre-Screening informed consent	X								
CCI CCI	X								
Genetic screening for RNF43 mutations	X								
Main study informed consent		X							
Demography & baseline characteristics		X							
Tumour genetic and PD-L1 staining history (optional)[j]		X							
CCI CCI (optional and only applicable if not previously collected during central pre-screening)		X							
Substance use (smoking and alcohol)		X							

	Module 1 (PDAC)– Schedule of assessments								
	Pre-Screening[t]	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycle)**	**IP Discontinuation**	**30 day follow-up**	**Survival follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
Medical/surgical history		X							
Oral and dental assessments [o]		X	Oral assessment at each visit if patient reports dysgeusia						
Inclusion/exclusion criteria[u]		X							
CCI CCI CCI CCI		X							
Physical examination		X	X	X		X	X	X	
Karnofsky performance status		X	X	X	X	X	X	X	
Pregnancy test (WOCBP only)		(X)	(X)	(X)		(X)			
Baseline and 'on treatment' tumour biopsies (mandatory)[a]		X			X[g]		X (optional at progression)		
Vital signs (including height and weight)[m]		X	X	X	X	X	X	X	
Clinical chemistry / Haematology		X	X	X	X	X	X	X	

	Module 1 (PDAC)– Schedule of assessments								
	Pre-Screening[t]	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycle)**	**IP Discontinuation**	**30 day follow-up**	**Survival follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
CCI		X	X	X		X	X	X	
ECG[w]		X	X	X	X	X[k]			
Blood samples for bone turnover biomarkers (β-CTX)		X			X	X			
DEXA scan		X				X[l]			
CCI CCI CCI			X		X	X			
CCI CCI			X		X	X			
CCI CCI			X		X	Cycle 2 only			
CCI CCI			X		X	X	X		
RXC004 PK[f]			X		X	X			
RECIST 1.1 assessments (CT or MRI)[i]		X	On study tumour assessments should occur q6w ± 1 week (relative to first dose of IP) for the first 54 weeks, followed by q12w ± 1 week until RECIST1.1 radiological progression[n]						
CCI (mandatory unless unavailable at site)[p]		X	On study CCI assessment should occur at week 6 ± 1 week and week 18 ± 1 week relative to first dose of IP.						
Vitamin D3 and Calcium supplements		Patients should commence 800 IU vitamin D3 (Cholecalciferol) QD and 1000-1500 mg calcium daily supplements from ICF signature until RXC004 discontinuation							

	Module 1 (PDAC)– Schedule of assessments								
	Pre-Screening[t]	**Screening**	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycle)**	**IP Discontinuation**	**30 day follow-up**	**Survival follow-up**
Window	**n/a**	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
Denosumab dosing[q]			120 mg SC denosumab once every month from C0D1 until RXC004 discontinuation						
RXC004 dosing[v]			X (2mg single dose)	Continuous daily dosing (2mg QD)					
RXC004 diary			X	Review at each visit			X		
Concomitant medication		X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	
Taste assessment[s]		X	At each visit - only if patient reports dysgeusia						
Survival status and post-discontinuation anti-cancer therapy[h]								X	X

a Screening (pre-first dose IP) biopsy is a mandatory requirement except in exceptional circumstances in which biopsy is not technically feasible. All patients without a baseline sample must be approved by the Sponsor before starting study treatment. The baseline CCI can be a 'fresh newly acquired' biopsy or an CCI (from the same site that 'on treatment' biopsy will be taken) and taken after completion of all prior standard of care treatments. In exceptional circumstances where baseline biopsy cannot be scheduled before C0D1, the procedure may be performed before C1D1 after a minimum of 4 days washout from C0D1. A second 'on treatment' biopsy at C1D15 (+ up to 7 days), is also mandatory providing that investigator judges the second biopsy to be technically and clinically feasible. An optional biopsy at progression is encouraged. The Cycle 1 Day 15 biopsy should be collected post-dose and the time of collection should be accurately recorded. RECIST 1.1 target lesions should not be chosen for biopsies.

b CCI

c CCI

d CCI

e CCI CCI .

f Blood samples for PK analysis should be collected as follows (the actual time for each blood draw must be accurately recorded);
Cycle 0: CCI
Cycle 1, CCI
Cycle X, CCI

g CCI

h Survival and details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected

i CT (preferred) or MRI, each preferably with IV contrast. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, scanner and

radiologist reading the measurements across all imaging time points per patient. The baseline RECIST1.1 scan should be performed within 6 weeks of the first dose of study treatment – preferably as close to the first dose as possible, but if scans were performed for alternate reasons prior to signing consent, these may be used for screening purposes to avoid unnecessary scans, if the patient consents, the scan(s) have been performed within 6 weeks of the first dose of study treatment and all the imaging requirements in the Imaging Acquisition Guidelines have been met.

j Optional collection of results from any previous tumour genetic screening and/or PD-1/PD-L1 staining. Results from genetic screening of the following genes will be collected from medical records and recorded in the study database: RNF43, TP53, BRCA1, BRCA2, and KRAS.

k ECGs should be performed on Cycle 2 Day 1 and as clinically indicated from Cycle 3 onwards.

l DEXA scans should be performed at screening, on Cycle 4 Day 1, Cycle 7 Day 1 and then every 7 RXC004 cycles thereafter (+/- 3-day window). T-score and bone mineral density for each of the following 3 sites, all of which must be assessed at screening: R/L total hip, R/L femoral neck, lumbar spine [L1-4]).

m Height is required at screening only.

n Symptomatically stable patients may continue study treatment after RECIST1.1 progression, until either symptomatic progression or second RECIST1.1 progression (relative to the first RECIST1.1 progression on study treatment), if agreed with the Sponsor. Patients who continue study treatment after RECIST1.1 progression should continue RECIST1.1 assessments as per protocol until discontinuation of study treatment. See Section 7.1.1 for more details.

o A dental examination with preventive dentistry if appropriate and an individual benefit-risk assessment is mandatory prior to treatment with denosumab. An initial dental examination may be performed by a member of the clinical team who can assess the need for referral to a dentist for further assessment including any preventative dentistry. A visual oral examination (including tongue, palate, uvula, tonsils, buccal mucosa, lips, gums and parotid duct) should also be performed at baseline and at each scheduled visit were dysgeusia is reported as an AE.

p CCI [redacted]

q All patients must receive denosumab before first dose of RXC004. 120 mg sc denosumab should be administered approximately once every month from C0D1 until RXC004 discontinuation. Investigators may delay subsequent denosumab doses until the next scheduled visit providing that there is no significant increase in β-CTX compared to baseline, according to Investigator judgement.

r CCI [redacted]

s A taste assessment (consisting of a specific set of questions) will be performed at screening and at each study visit when patient reports dysgeusia. Please see Section 8.3.12 for more details.

t Pre-screening is not mandatory for patients with prior documented evidence of a loss of function RNF43 mutation from a panel approved by the Sponsor.

u If available, the last 2 imaging scans taken prior to the screening scan for this study and/or their reports may be requested for central/sponsor review.

v Patients must fast (water to drink only) for at least 2 hours prior to taking a dose to at least 1 hour post-dose for all doses.

w Triplicate ECGs should be collected as follows;
Cycle 0: CCI [redacted]
Cycle 1, CCI [redacted]
Cycle X, CCI [redacted]
At selected sites, ambulatory Holter monitoring will be used on Cycle 0 Day 1 and Cycle 1 Day 15 for central analysis of digital ECG information.

C, Cycle; CT, computerised tomography CCI [redacted]; D, Day; ECG, electrocardiogram; CCI [redacted]; IP, investigational product; IV, intravenous; MRI, magnetic resonance imaging; CCI [redacted] PK, pharmacokinetic(s); QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SC, subcutaneous; WOCBP, women of child-bearing potential.

10.9 Statistical Considerations

General statistical considerations can be found in Section 9.

10.9.1 Module 1 Sample Size Determination

The method by Frewer et al (Frewer et al 2016), together with the totality of the data collected, will be used to guide go/no-go decision making:

For the population under investigation, the standard of care of liposomal irinotecan in combination with 5-FU/Leucovorin showed a 6-month PFS rate of CCI% (NAPOLI-1 trial, Wang-Gillam et al 2016), which will be the CCI in our study. An improvement to CCI% in 6-month PFS would be considered clinically significant in this patient population (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 patients or fewer 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.

Note: "Enrolled" means the subject has completed the main study CRF and has been assigned to a treatment arm.

MODULE 2 (BTC)

11 MODULE 2 (RXC004 MONOTHERAPY IN BILIARY TRACT CANCER)

11.1 Background

Biliary tract cancer represents 3% of gastro-intestinal malignancies and is the commonest hepatobiliary malignancy and includes gallbladder (GBC), ampulla of Vater (AVC), and intra-hepatic and extrahepatic cholangiocarcinoma (CCA).

The incidence of biliary tract cancer varies hugely with some regions depicting high prevalence accounted for by high liver fluke infestations where cholangiocarcinoma is more common. Areas with a high prevalence of cholelithiasis correspond to a high prevalence of GBC. Regions where these risk factors are absent have a low incidence of biliary tract cancer.

Approximately 30-40% of patients with newly diagnosed biliary tract cancer have disease that is amenable to curative intent surgery. Adjuvant capecitabine has demonstrated a survival advantage (Primrose et al 2019) with a median overall survival of 51 months compared to 36 months with observation alone. Despite this, the prognosis for BTC remains extremely poor with a 5-year survival rate of approximately 2%. Standard of care treatment of newly diagnosed metastatic BTC is gemcitabine in combination with cisplatin which demonstrated an overall survival of 11.7 months compared to 8.1 months with gemcitabine monotherapy (Valle et al 2010). Recently modified FOLFOX (mFOLFOX) in addition to active symptom control reported a median survival of 6.2 months compared to 5.3 months with active symptom control alone in the 2nd line setting (Lamarca et al 2019)

Approximately 50% of cholangiocarcinomas have known molecular alterations/mutations. A trial of pemigatinib, a fibroblast growth factor receptor (FGFR)-2 inhibitor was evaluated in 2nd/3rd line metastatic cholangiocarcinoma patients with FGFR-2 fusions and reported a 36% ORR and a medium survival of 21 months (Abou-Alfa et al 2020). FGFR2 mutations are exclusively found in intra-hepatic CCA (ICC) and are present in approx. 13% of ICC patients. Ivosidenib, an isocitrate dehydrogenase (IDH)-1 inhibitor reported a median OS of 10.8 months in 2nd/3rd line metastatic cholangiocarcinoma patients with IDH1 mutations. Similar to FGFR2 mutations, IDH1 mutations are found in 15% of CCA patients (Abou-Alfa et al 2020); these genetic aberrations are usually mutually exclusive.

11.2 Module 2 Rationale

RXC004 is a small molecule PORCN inhibitor which reduces Wnt signalling and therefore may offer an opportunity to deliver clinical benefit in tumours that have aberrantly activated Wnt signalling.

While downstream Wnt pathway mutations are rare in cholangiocarcinoma, patient samples have been shown to overexpress Wnt ligands. IHC of patient samples showed Wnt3a, Wnt5a, and Wnt7b were positive in 92.1, 76.3, and 100 % of 38 CCA tissues (Loilome et al 2014). In a separate study of 37 patients, Wnt7B and Wnt10A mRNA was found to be significantly higher in CCA when compared to healthy tissue (Boulter et al 2015). High expression of Wnt5a was associated with worse prognosis (Loilome et al 2014).

Porcupine inhibitors have been reported to be anti-proliferative in several human cholangiocarcinoma cancer cell lines both *in vitro* and *in vivo* (Boulter et al 2015 and Noll et al 2016). In addition, porcupine inhibitors have demonstrated efficacy in two *in-vivo* preclinical biliary cancer models, a GEM model and a TAA-induced rat model (Boulter et al 2015).

RXC004 may offer an opportunity to deliver clinical benefit in patients with advanced (unresectable)/metastatic biliary tract cancer that has progressed following 1st-line standard of care treatment, where there is currently still a high unmet need.

11.3 Benefit-Risk Assessment

11.3.1 RXC004 Risks

The risk assessment for RXC004 monotherapy treatment can be found in Section 2.3.1.

11.3.2 Benefit Assessment

This Module will evaluate RXC004 monotherapy in advanced (unresectable)/metastatic biliary tract cancer patients who have received one prior approved standard of care systemic treatment. RXC004 monotherapy may offer clinical benefit by both a direct tumour targeting mechanism and by an immune-oncology mechanism.

Treatment outcome for advanced (unresectable)/metastatic biliary tract cancer remains poor. First line metastatic treatment of patients with advanced BTC with standard of care gemcitabine in combination with cisplatin or gemcitabine monotherapy results in an overall survival in the range of 8-13 months (Valle et al 2010 and Valle et al 2020). Furthermore, the recently reported Phase 3 TOPAZ-1 study demonstrated that the addition of the PD-L1 inhibitor durvalumab to cisplatin and gemcitabine chemotherapy significantly improved overall survival compared with placebo plus chemotherapy in patients with advanced BTC, with HR 0.80 (95% CI: 0.66, 0.97); p = 0.021 (Oh et al 2022). Modified FOLFOX (mFOLFOX) in addition to active symptom control showed a median survival of 6.2 months compared to 5.3 months with active symptom control alone in the 2nd-line setting (Lamarca et al 2019). The hazard ratio reported was 0.69 representing a 31% reduction in the risk of death. However, not all patients are considered fit enough to receive mFOLFOX as 2nd-line therapy.

Porcupine inhibitors have been reported to be anti-proliferative in several human biliary

cancer cell lines both *in vitro* and *in vivo* (Noll et al 2016, Boulter et al 2015). In addition, porcupine inhibitors have demonstrated efficacy in two *in-vivo* preclinical biliary cancer models, a GEM model and a TAA-induced rat model (Boulter et al 2015). Patient samples have been shown to overexpress Wnt ligands. Two studies have already looked at limited Wnt ligands in a small set of patients. IHC of patient samples in the first study showed Wnt3a, Wnt5a, and Wnt7b were positive in 92.1%, 76.3%, and 100%, respectively of 38 cholangiocarcinoma tissues (Loilome et al 2014). In a second study of 37 patients, Wnt7B and Wnt10A mRNA was found to be significantly higher in biliary cancer when compared to healthy tissue (Boulter et al 2015). High expression of Wnt5a was associated with worse prognosis (Loilome et al 2014).

The Phase 1 study of RXC004 enrolled unselected patients with advanced cancers with a median of three prior lines of treatment. Out of 18 RECIST-evaluable patients, five had SD, in one case lasting for up to 26 weeks. All five of these patients with SD had Wnt-ligand-dependent tumours (three of which were BTC), supporting the hypothesis that RXC004 will have clinical activity in selected tumours that are dependent on Wnt ligand signalling pathways (Cook et al 2021).

Given this preclinical and clinical evidence of involvement of the Wnt pathway in cholangiocarcinoma there is a clear rationale to assess RXC004 monotherapy in advanced (unresectable)/metastatic biliary tract cancer patients.

11.4 Objectives and endpoints

The objectives and endpoints for Module 2 can be found in Section 3.

11.5 Module 2 Study Design

Module 2 is an open label, multicentre module to evaluate the preliminary efficacy and safety of RXC004 monotherapy in patients with advanced (unresectable)/metastatic BTC, that has progressed following 1st line standard of care treatment.

Two dose levels of RXC004 will be evaluated in this Module. In Cohort 1, patients will receive RXC004 2 mg QD. Cohort 2 will evaluate a lower dose of RXC004 1 mg QD, depending on the emerging data observed with the 2 mg dose in Cohort 1. Should the 2 mg fail to show any anti-tumour activity in Cohort 1 that warrants further investigation, as per Section 11.9.1, then this lower dose cohort will not open unless the SMC consider that tolerability issues on 2 mg have compromised the ability to show efficacy. If Module 3 (pembrolizumab combination) and Cohort 2 are open at the same time, then Module 3 will be prioritised, i.e. patients who are eligible for Module 3 should be assigned to Module 3 and not to Cohort 2 of Module 2.

CCI evaluable patients will be enrolled within each cohort of this module (see Table 14 for

definition of evaluable patients).

The primary objective of the module is to assess the preliminary efficacy of RXC004 in terms of 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 until radiological disease progression (as defined by RECIST1.1). Following radiological progression, patients will be followed-up for safety and survival.

The rationale for the study design and endpoints can be found in Section 4. The general study design is summarised in Figure 1.

11.5.1 Rationale for Primary Endpoint

Preclinical data indicate that RXC004 monotherapy used in an advanced (unresectable)/metastatic BTC population may deliver clinical benefit by a predominantly cytostatic rather than cytotoxic mechanism. Therefore, Progression Free Survival (PFS) rate at 6-months is a more appropriate endpoint than e.g. Objective Response Rate (ORR) in evaluating the potential clinical benefit of RXC004 monotherapy. A median PFS rate of 4 months and disease control rate of 33% with current standard of care 2nd line mFOLFOX have been reported in a Phase 3 randomised trial (Lamarca et al 2019).

11.5.2 Rationale for Secondary Endpoints

DCR, ORR, PFS, OS and % change in target lesions are appropriate endpoints in an advanced (unresectable)/metastatic cholangiocarcinoma patient population, and have been widely used and reported in clinical trials in this population.

11.6 Module 2 Patient Population

The study will recruit male or female patients aged 18 years or older with histologically documented, advanced (unresectable)/metastatic BTC that have progressed after 1 prior systemic standard of care treatment for advanced (unresectable)/metastatic BTC and have a minimum life expectancy of 12 weeks.

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

11.6.1 Inclusion Criteria

Core- and Module 2-specific inclusion criteria can be found in Sections 5.1 and 5.3, respectively. Participants are eligible to be included in the study only if all of the core and Module 2-specific following criteria are met.

11.6.2 Exclusion Criteria

Core exclusion criteria can be found in Section 5.4. There are no Module 2-specific exclusion

criteria. Participants are excluded from the study if any of the core exclusion criteria are met.

11.6.3 Lifestyle Considerations

Lifestyle considerations can be found in Section 5.6.

11.7 Study Treatment

Details of RXC004 monotherapy treatment can be found in Section 6. Discontinuation criteria for RXC004 can be found in Section 7.

11.8 Study Assessments

General details of the study assessment and procedures for Cohorts 1 and 2 of Module 2 can be found in Section 8.

11.8.1 Schedule of Assessments

Table 16 Module 2 (BTC) Schedule of Assessments

	Module 2 (BTC) Schedule of Assessments							
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day Follow-up**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
Main study informed consent	X							
Demography & baseline characteristics	X							
Tumour genetic and PD-L1 staining history (optional)[h]	X							
CCI CCI (mandatory if available)	X							
Substance use (smoking and alcohol)	X							
Medical/surgical history	X							
Oral and dental assessment[o]	X	Oral assessment at each visit - only if patient reports dysgeusia						
Inclusion/exclusion criteria[r]	X							
CCI CCI CCI CCI	X							
Physical examination	X	X	X		X	X	X	

	Module 2 (BTC) Schedule of Assessments							
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day Follow-up**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
ECOG performance status	X	X	X	X	X	X	X	
Pregnancy test (WOCBP only)	(X)	(X)	(X)		(X)			
Tumour biopsy (mandatory)[a]	X			X[l]		X (optional at progression)		
Vital signs (including height and weight)[i]	X	X	X	X	X	X	X	
Clinical chemistry / Haematology	X	X	X	X	X	X	X	
ECG[u]	X	X	X	X	X[k]			
DEXA Scan	X				X[m]			
CCI	X	X	X		X	X	X	
Blood samples for bone turnover biomarkers (β-CTX)	X			X	X			
CCI CCI		X		X	X			
CCI		X		X	X			
CCI CCI		X		X	Cycle 2 only			
CCI CCI		X		X	X	X		
RECIST 1.1 assessments (CT or MRI)[j]	X	On study tumour assessments should occur q6w ± 1 week (relative to first dose of IP) for the first 54 weeks, followed by q12w ± 1 week until RECIST1.1 radiological progression[n]						

	Module 2 (BTC) Schedule of Assessments							
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day Follow-up**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**q6w ± 1 week**
CCI [redacted] (mandatory unless unavailable at site)[p]	X	On study CCI [redacted] assessment should occur at week 6 ± 1 week and week 18 ± 1 week relative to first dose of IP.						
Vitamin D3 and Calcium supplements	Patients should commence 800 IU vitamin D3 (Cholecalciferol) QD and 1000-1500 mg calcium daily supplements from ICF signature until RXC004 discontinuation							
Denosumab dosing[q]		120 mg SC denosumab once every month from C0D1 until RXC004 discontinuation						
RXC004 dosing[t]		X (2mg single dose in Cohort 1; 1mg single dose in Cohort 2)	Continuous daily dosing (2mg QD in Cohort 1; 1mg QD in Cohort 2)					
RXC004 diary		X	Review at each visit			X		
RXC004 PK[f]		X		X	X			
Concomitant medication	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	
Taste assessment[s]	X	At each visit – only if patient reports dysgeusia						
Survival status and post-discontinuation anti-cancer therapy[g]							X	X

a Screening (pre-first dose IP) biopsy is a mandatory requirement except in exceptional circumstances where biopsy is not technically feasible. All patients without a baseline sample must be approved by the Sponsor before starting study treatment. The baseline CCI [redacted] can be a 'fresh newly acquired' biopsy or an CCI [redacted] (from the same site that 'on treatment' biopsy will be taken) and taken after completion of all prior standard of care treatments. In exceptional circumstances where baseline biopsy cannot be scheduled before C0D1, the procedure may be performed before C1D1 after a minimum of 4 days washout from C0D1. A second 'on treatment' biopsy at C1D15 (+ up to 7 days), is also mandatory providing that investigator judges the second biopsy to be technically and clinically feasible. An optional biopsy at progression is encouraged. The Cycle 1 Day 15 biopsy should be collected post-dose and the time of collection should be accurately recorded. RECIST 1.1 target lesions should not be chosen for biopsies.

b CCI [redacted]

c CCI [redacted]

d CCI [redacted]

e CCI
CCI
f Blood samples for PK analysis should be collected as follows (the actual time for each blood draw must be accurately recorded):
Cycle 0: CCI
Cycle 1, CCI
Cycle X, CCI
g Survival and details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.
h Optional collection of results from any previous tumour genetic screening and/or PD-1/PD-L1 staining. Results from genetic screening of the following genes will be collected from medical records and recorded in the study database; FGFR2, IDH1, IDH2, RNF43, ARID1A, BAP1, PBRM1, PINK3A, CDKN2A, TP53, MAP2K1, SMAD4, BRAF, KRAS and PTEN.
i Height is required at screening only.
j CT (preferred) or MRI, each preferably with IV contrast. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, scanner and radiologist reading the images across all imaging time points per patient. The baseline RECIST1.1 scan should be performed within 6 weeks of the first dose of study treatment – preferably as close to the first dose as possible, but if scans were performed for alternate reasons prior to signing consent, these may be used for screening purposes to avoid unnecessary scans, if the patient consents, the scan(s) have been performed within 6 weeks of the first dose of study treatment and all the imaging requirements in the Imaging Acquisition Guidelines have been met.
k ECGs should be performed on Cycle 2 Day 1 and as clinically indicated from Cycle 3 onwards.
l + 7-day window.
m DEXA scans should be performed at screening, on Cycle 4 Day 1, Cycle 7 Day 1 and then every 7 RXC004 cycles thereafter (± 3-day window). T-score and bone mineral density for each of the following 3 sites, all of which must be assessed at screening: R/L total hip, R/L femoral neck, lumbar spine [L1-4]).
n Symptomatically stable patients may continue study treatment after RECIST1.1 progression, until either symptomatic progression or second RECIST1.1 progression (relative to the first RECIST1.1 progression on study treatment), if agreed with the Sponsor. Patients who continue study treatment after RECIST1.1 progression should continue RECIST1.1 assessments as per protocol until discontinuation of study treatment. See Section 7.1.1 for more details.
o A dental examination with preventive dentistry if appropriate and an individual benefit-risk assessment is mandatory prior to treatment with denosumab. An initial dental examination may be performed by a member of the clinical team who can assess the need for referral to a dentist for further assessment including any preventative dentistry. A visual oral examination (including tongue, palate, uvula, tonsils, buccal mucosa, lips, gums and parotid duct) should also be performed at baseline and at each scheduled visit were dysgeusia is reported as an AE.
p CCI
CCI
CCI
CCI
q All patients must receive denosumab before first dose of RXC004. 120 mg SC denosumab should be administered approximately once every month from C0D1 until RXC004 discontinuation. Investigators may delay subsequent denosumab doses until the next scheduled visit providing that there is no significant increase in β-CTX compared to baseline, according to Investigator judgement.
r If available, the last 2 imaging scans taken prior to the screening scan for this study and/or their reports may be requested for central/sponsor review.
s A taste assessment (consisting of a specific set of questions) will be performed at screening and at each study visit when patient reports dysgeusia. Please see Section 8.3.12 for more details
t Patients must fast (water to drink only) for at least 2 hours prior to taking a dose to at least 1-hour post-dose for all doses.
u Triplicate ECGs should be collected as follows;
Cycle 0: CCI
Cycle 1, CCI
Cycle X, CCI
At selected sites, ambulatory Holter monitoring will be used on Cycle 0 Day 1 and Cycle 1 Day 15 for central analysis of digital ECG information.

BTC, biliary tract cancer; C, Cycle; CT, computerised tomography; CCI ; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; CCI ; IP, investigational product; IV, intravenous; MRI, magnetic resonance imaging; PK, pharmacokinetic(s); QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SC, subcutaneous; WOCBP, women of child-bearing potential.

11.9 Statistical Considerations

General statistical considerations can be found in Section 9.

11.9.1 Module 2 Sample Size Determination

The method by Frewer et al (Frewer et al 2016), together with the totality of the data collected, will be used to guide go/no-go decision making.

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
CCI
CCI
CCI. If CCI or fewer patients 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 month 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 each cohort in order for CCI patients to be evaluable.

12 MODULE 3 (BILIARY TRACT CANCER) – RXC004 COMBINATION THERAPY WITH PEMBROLIZUMAB

12.1 Background

Background information on BTC, including currently available treatments and survival rates, is provided in Section 11.1.

12.2 Module 3 Rationale

As described in Section 11.3.2, a significant unmet medical need remains for improved treatment outcomes in patients with advanced (unresectable)/metastatic BTC.

Results from preclinical and clinical studies suggest that porcupine inhibitors may be a potentially effective treatment for tumour types that are dependent on Wnt ligand signalling pathways, as detailed in Section 2.2. Evidence suggests that Wnt-ligand pathway activity drives the immune evasion of tumours and is implicated in both intrinsic and adaptive resistance to immunotherapy (Luke et al 2019, Spranger and Gajewski 2018). In order for immune cells to recognise cancer cells, they must first infiltrate the tumour and then remain activated. Wnt pathway activation (β-catenin positive cells) and Wnt ligand signalling is correlated with reduced CD8+ve T-cell infiltration (Spranger and Gajewski 2018), and primary immune checkpoint inhibitor resistance in multiple cancers including BTC (Luke et al 2019).

RXC004 has demonstrated an immune stimulant effect and efficacy in combination with an anti-PD-1 antibody in mouse syngeneic tumour models, which supports testing of the combination of RXC004 with pembrolizumab (see current RXC004 IB).

12.3 Benefit-Risk Assessment

12.3.1 Risks: RXC004 in Combination with Pembrolizumab

Toxicities from treatment with immune checkpoint inhibitors, including mAbs targeting PD-1 and its ligand PD-L1, and CTLA4, frequently include irAEs, and can involve any organ or system (Haanen et al 2017). AEs associated with pembrolizumab exposure may represent an immunological aetiology. Guidelines for dose modification and toxicity management for irAEs associated with pembrolizumab are provided in Appendix L 1. More detailed information about the known and expected benefits and risks of pembrolizumab may be found in the pembrolizumab prescribing information.

Pembrolizumab has been evaluated as monotherapy in patients with advanced BTC in 2 studies (KEYNOTE-028 and KEYNOTE-158); see Section 2.2.4. The safety profile observed in these studies was considered manageable, and no new safety signals were identified. Most AEs were mild-to-moderate in severity. Grade 3 to 5 treatment-related AEs

were reported in 14 (13.5%) of patients in KEYNOTE-158 (no grade 4; 1 patient had grade 5 renal failure), and in 4 (16.7%) in KEYNOTE-028 (no grade 4/5) (Piha-Paul et al 2020).

RXC004 in combination with pembrolizumab

RXC004 has not previously been administered in combination with pembrolizumab; however, the combination of RXC004 with the anti-PD-1 nivolumab has been evaluated in an ongoing Phase 1 study, and the safety data suggest that the combination is tolerated at RXC004 doses of 1 mg QD and 1.5 mg QD (see Section 4.4.1.2).

The monotherapy toxicity profiles of RXC004 and pembrolizumab are generally non overlapping except for colitis (see Section 2.3.1.2).

Combination treatment with the PORCN inhibitor WNT974 with the anti-PD-1 monoclonal antibody spartalizumab in a Phase 1 study in patients with advanced solid tumours was reported to be well tolerated (see Section 2.2.2).

The safety profile of RXC004 in combination with pembrolizumab is anticipated to be similar to that of RXC004 in combination with nivolumab, and of WNT974 in combination with spartalizumab in patients with advanced solid tumours.

Specific exclusion criteria, safety laboratory assessments, monitoring for irAEs, and colitis/toxicity management guidelines are included in this protocol to mitigate the risks with the combination of RXC004 and pembrolizumab.

12.3.2 Benefit Assessment

Module 3 will evaluate RXC004 given in combination with pembrolizumab in patients with advanced (unresectable)/metastatic BTC who have received one prior approved standard of care systemic treatment.

Given the available evidence for the involvement of the Wnt pathway in cholangiocarcinoma, it is hypothesised that patients with advanced (unresectable)/metastatic BTC may benefit from treatment with RXC004. Pembrolizumab has demonstrated anti-tumour activity in patients with advanced BTC who had no other options for standard therapy. The combination of RXC004 with pembrolizumab may offer greater clinical benefit than either agent alone, via both a direct RXC004 based effect on tumour cell growth and a synergistic effect with pembrolizumab on the immune system.

12.4 Objectives and Endpoints

The objectives and endpoints for Module 3 are identified in Section 3.

12.5 Module 3 Study Design

Module 3 is an open-label multicentre module to evaluate the preliminary efficacy and safety of RXC004 in combination with pembrolizumab in patients with advanced (unresectable)/metastatic BTC, that has progressed following first-line SoC treatment.

An estimated CCI patients will be enrolled in this module to obtain CCI evaluable patients (see Table 14 for the definition of evaluable patients). A safety review of the combination data will be conducted by the SMC after CCI patients have received the combination of RXC004 and pembrolizumab for at least 1 cycle.

The primary objective of this module is to assess the preliminary efficacy of RXC004 in terms of ORR by RECIST 1.1. Tumour assessment will be performed by Investigators q6w ± 1 week (relative to the date of initiation of study treatment) for the first 54 weeks, followed by q12w until radiological disease progression (as defined by RECIST1.1). Following radiological progression, patients will be followed-up for safety and survival.

If Module 3 and Cohort 2 of Module 2 are open at the same time, then Module 3 will be prioritised, i.e. patients who are eligible for Module 3 should be assigned to Module 3 and not to Cohort 2 of Module 2.

The rationale for the study design and endpoints can be found in Section 4. The overall study design is summarised in Figure 1.

12.5.1 Rationale for Primary Endpoint

The combination of RXC004 with pembrolizumab is expected to result in both a RXC004-based effect on tumour cell growth and a synergistic effect with pembrolizumab on the immune system. RXC004 should reverse Wnt pathway-induced immune evasion and pembrolizumab will allow activated CD8 T cells to function without the immune suppression resulting from tumour PD-L1 expression. Therefore, it is anticipated that with combination therapy, the active CD8 T cells will destroy tumour cells and shrink the size of the tumour; hence, ORR is considered to be an appropriate primary endpoint for Module 3.

Furthermore, ORR was selected as the primary endpoint for the pembrolizumab single-arm monotherapy studies KEYNOTE-028 and KEYNOTE-158 in patients with advanced BTC (Piha-Paul et al 2020), and responses have been observed in these studies with an ORR of 13.0% (3/23) and 5.8% (6/104), respectively. Therefore, improving this ORR is considered an appropriate primary objective, with these studies providing an objective benchmark.

12.5.2 Rationale for Secondary Endpoints

DCR, PFS, OS, and % change in target lesions are appropriate endpoints in an advanced (unresectable)/metastatic cholangiocarcinoma patient population, and have been widely used

and reported in clinical studies in this population.

12.5.3 Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 400 mg q6w.

A 400 mg q6w dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg every 3 weeks (q3w), in all treatment settings in which 200 mg q3w pembrolizumab is currently appropriate (Lala et al 2020). Specifically, the dosing regimen of 400 mg q6w for pembrolizumab is considered adequate based on modelling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg q6w is similar to that at the approved 200 mg q3w dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg q6w are generally within the range of those achieved with 2 mg/kg or 200 mg q3w in the majority (> 99%) of patients.
  - Peak concentrations (C_{max}) at 400 mg q6w are well below the C_{max} for the highest clinically tested dose of 10 mg/kg q2w, supporting that the safety profile for 400 mg q6w should be comparable to the established safety profile of pembrolizumab.
  - Exposure-response for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg q6w is expected to be similar to that at 200 mg or 2 mg/kg q3w, given the similar exposures; thus 400 mg q6w is expected to be efficacious across indications.

12.6 Module 3 Patient Population

Module 3 of the study will recruit male or female patients aged 18 years or older with histologically documented, advanced (unresectable)/metastatic BTC that have progressed after one prior systemic standard of care treatment for advanced (unresectable)/metastatic BTC and have a minimum life expectancy of 12 weeks.

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

12.6.1 Inclusion Criteria

The Core- and BTC module-specific inclusion criteria can be found in Sections 5.1 and 5.3, respectively. Patients are eligible to participate in Module 3 only if all of the core and

BTC-specific criteria are met.

12.6.2 Exclusion Criteria

Core exclusion criteria can be found in Section 5.4. The Module 3-specific exclusion criteria are provided in Section 5.5. Patients are excluded from Module 3 if they meet any of the core exclusion criteria or any of the Module 3-specific exclusion criteria.

12.6.3 Lifestyle Considerations

Lifestyle considerations can be found in Section 5.6.

12.7 Study Treatment

12.7.1 Study Treatment(s) Administered

Details of RXC004 and denosumab treatment, which are administered in all Modules of the study, can be found in Section 6. Details of pembrolizumab study treatment for Module 3 are provided in Table 17.

Table 17 Study Interventions: Pembrolizumab

Intervention name	Dosage formulation	Unit dose strength	Dosage level	Route of administration	Regimen/ Treatment period	Sourcing
Pembrolizumab (MK-3475)	Solution for infusion	100 mg/vial	400 mg every 6 weeks	IV infusion	Treatment continues until participant meets a criterion for discontinuation (see Section 7)	Provided centrally by Sponsor

IV, intravenous.

RXC004 study treatment is administered in 21-day cycles, in combination with pembrolizumab q6w (i.e., pembrolizumab is dosed on alternate cycles). Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each alternate cycle due to administrative reasons.

RXC004 is to be administered 30-60 minutes after administration of pembrolizumab.

Discontinuation criteria can be found in Section 7.

12.7.2 Preparation/Handling/Storage/Accountability of Study Treatments

Details for RXC004 and denosumab are provided in Section 6.2.

Pembrolizumab will be supplied as 25 mg/mL concentrate for solution for infusion, 100 mg/4 mL vial.

Storage of pembrolizumab:

The Investigator, or an appropriate delegate, must ensure that study treatment is stored in a secured area, at appropriate temperatures and as specified on the label, and in accordance with applicable regulatory requirements.

Store unopened pembrolizumab vials in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light.

Preparation and administration of the pembrolizumab infusion:

- The dose of pembrolizumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique.
- Do not shake the vial. Equilibrate the vial to room temperature (at or below 25°C). Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an IV bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 mL (total content per vial 4.25 mL) to ensure the recovery of 4 mL of concentrate. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of pembrolizumab has been demonstrated for 96 hours at 2ºC to 8ºC. This 96-hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or IV bags must be allowed to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in diluted solution. Administer the infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 μm in-line or add-on filter.
- Do not co-administer other medicinal products through the same infusion line.
- Pembrolizumab for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12.7.3 Study Treatment Compliance

For details of compliance with RXC004, see Section 6.3.

Pembrolizumab will be dosed at the site, directly from the investigator or designee, under medical supervision. The date, and start and end times of the dose administered at site will be recorded in the source documents and recorded in the eCRF. The dose of pembrolizumab and the study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

12.7.4 Pembrolizumab Dose Modification and Toxicity Management

Guidelines for pembrolizumab dose modification and toxicity management are provided in Appendix L, as follows:

- Dose modification and toxicity management for irAEs associated with pembrolizumab: Appendix L 1
- Dose modification and toxicity management of infusion reactions related to pembrolizumab: Appendix L 2
- Other allowed dose interruption for pembrolizumab: Appendix L 3.

12.8 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunological aetiology are outlined along with the dose modification guidelines in Appendix L 1.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Appendix L 1 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

12.9 Study Assessments

Table 18 presents the SoA for Module 3.

Table 18 Module 3 (BTC) Schedule of Assessments, RXC004 + Pembrolizumab

	Module 3 (BTC) Schedule of Assessments								
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day follow-up[v]**	**90-day follow-up[v]**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**± 3d**	**q6w ± 1 week**
Main study informed consent	X								
Demography & baseline characteristics	X								
Tumour genetic and PD-L1 staining history (optional)[h]	X								
CCI CCI (mandatory if available)[y]	X								
Substance use (smoking and alcohol)	X								
Medical/surgical history	X								
Oral and dental assessment[o]	X	Oral assessment at each visit - only if patient reports dysgeusia							
Inclusion/exclusion criteria[r]	X								
HIV, HepB, HepC testing	X								
CCI CCI CCI CCI	X								
Physical examination	X	X	X		X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	

	Module 3 (BTC) Schedule of Assessments								
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day follow-up[v]**	**90-day follow-up[v]**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**± 3d**	**q6w ± 1 week**
Pregnancy test (WOCBP only)	(X)[z]	(X)	(X)		(X)				
Tumour biopsy (mandatory)[a]	X			X[l]		X (optional at progression)			
Vital signs (including height and weight)[i]	X	X	X	X	X	X	X		
Clinical chemistry / Haematology	X	X	X	X	X	X	X	X	
Thyroid function tests[w]	X		X	X	X	X	X	X	
ECG[u]	X	X	X	X	X[k]				
DEXA Scan	X				X[m]				
CCI	X	X	X		X	X	X		
Blood samples for bone turnover biomarkers (β-CTX)	X			X	X				
CCI CCI		X		X	X				
CCI		X		X	X				
CCI CCI		X		X	Cycle 2 only				
CCI CCI		X		X	X	X			
RECIST 1.1 assessments (CT or MRI)[j]	X	On study tumour assessments should occur q6w ± 1 week (relative to first dose of IP) for the first 54 weeks, followed by q12w ± 1 week until RECIST1.1 radiological progression[n]							
CCI (mandatory unless unavailable at site)[p]	X	On study CCI assessment should occur at week 6 ± 1 week and week 18 ± 1 week relative to first dose of IP.							

	Module 3 (BTC) Schedule of Assessments								
	Screening	**Cycle 0 (3-7 days)**	**Cycle 1 (21-day cycle)**		**Cycle X Day 1 (21-day cycles)**	**IP Discontinuation**	**30 day follow-up[v]**	**90-day follow-up[v]**	**Survival follow-up**
Window	**-28 to –1**	**D1**	**D1**	**D15 ± 1d**	**± 3d**	**Within 7 days of discontinuation**	**± 3d**	**± 3d**	**q6w ± 1 week**
Vitamin D3 and calcium supplements	Patients should commence 800 IU vitamin D3 (cholecalciferol) QD and 1000-1500 mg calcium daily supplements from informed consent form signature until RXC004 discontinuation								
Denosumab dosing[q]		120 mg SC denosumab once every month from C0D1 until RXC004 discontinuation							
RXC004 dosing[t]		X (1.5 mg single dose)	Continuous daily dosing (1.5 mg QD)						
RXC004 diary		X	Review at each visit			X			
Pembrolizumab dosing (400 mg IV) [x]			X		X q6w ±3 days from C1D1 (ie, dosed on alternate cycles)				
RXC004 PK[f]		X		X	X				
Concomitant medication	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	
Taste assessment[s]	X	At each visit – only if patient reports dysgeusia							
Survival status and post-discontinuation anti-cancer therapy[g]							X	X	X

[a] Screening (pre-first dose IP) biopsy is a mandatory requirement except in exceptional circumstances where biopsy is not technically feasible. All patients without a baseline sample must be approved by the Sponsor before starting study treatment. The baseline CCI can be a 'fresh newly acquired' biopsy or an CCI (from the same site that 'on treatment' biopsy will be taken) and taken after completion of all prior standard of care treatments. In exceptional circumstances where baseline biopsy cannot be scheduled before C0D1, the procedure may be performed before C1D1 after a minimum of 4 days washout from C0D1. A second 'on treatment' biopsy at C1D15 (+ up to 7 days), is also mandatory providing that investigator judges the second biopsy to be technically and clinically feasible. An optional biopsy at progression is encouraged. The Cycle 1 Day 15 biopsy should be collected post-dose and the time of collection should be accurately recorded. RECIST 1.1 target lesions should not be chosen for biopsies.

b CCI

CCI

CCI

CCI

CCI

Blood samples for PK analysis should be collected as follows (the actual time for each blood draw must be accurately recorded):
Cycle 0: CCI

CCI

Cycle 1, CCI

CCI

Cycle X, CCI

g Survival and details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

h Optional collection of results from any previous tumour genetic screening and/or PD-1/PD-L1 staining. Results from genetic screening of the following genes will be collected from medical records and recorded in the study database; FGFR2, IDH1, IDH2, RNF43, ARID1A, BAP1, PBRM1, PINK3A, CDKN2A, TP53, MAP2K1, SMAD4, BRAF, KRAS and PTEN.

i Height is required at screening only.

j CT (preferred) or MRI, each preferably with IV contrast. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, scanner and radiologist reading the images across all imaging time points per patient. The baseline RECIST1.1 scan should be performed within 6 weeks of the first dose of study treatment – preferably as close to the first dose as possible, but if scans were performed for alternate reasons prior to signing consent, these may be used for screening purposes to avoid unnecessary scans, if the patient consents, the scan(s) have been performed within 6 weeks of the first dose of study treatment and all the imaging requirements in the Imaging Acquisition Guidelines have been met.

k ECGs should be performed on Cycle 2 Day 1 and as clinically indicated from Cycle 3 onwards.

l + 7-day window.

m DEXA scans should be performed at screening, on Cycle 4 Day 1, Cycle 7 Day 1 and then every 7 RXC004 cycles thereafter (± 3-day window). T-score and bone mineral density for each of the following 3 sites, all of which must be assessed at screening: R/L total hip, R/L femoral neck, lumbar spine [L1-4]).

n Symptomatically stable patients may continue study treatment after RECIST1.1 progression, until either symptomatic progression or second RECIST1.1 progression (relative to the first RECIST1.1 progression on study treatment), if agreed with the Sponsor. Patients who continue study treatment after RECIST1.1 progression should continue RECIST1.1 assessments as per protocol until discontinuation of study treatment. See Section 7.1.1 for more details.

o A dental examination with preventive dentistry if appropriate and an individual benefit-risk assessment is mandatory prior to treatment with denosumab. An initial dental examination may be performed by a member of the clinical team who can assess the need for referral to a dentist for further assessment including any preventative dentistry. A visual oral examination (including tongue, palate, uvula, tonsils, buccal mucosa, lips, gums and parotid duct) should also be performed at baseline and at each scheduled visit were dysgeusia is reported as an adverse event.

p CCI

CCI

CCI

CCI

q All patients must receive denosumab before first dose of RXC004. Denosumab 120 mg SC should be administered approximately once every month from C0D1 until RXC004 discontinuation. Investigators may delay subsequent denosumab doses until the next scheduled visit providing that there is no significant increase in β-CTX compared to baseline, according to Investigator judgement.

r If available, the last 2 imaging scans taken prior to the screening scan for this study and/or their reports may be requested for central/sponsor review.

s A taste assessment (consisting of a specific set of questions) will be performed at screening and at each study visit when patient reports dysgeusia. Please see Section 8.3.12 for more details.

[t] Patients must fast (water to drink only) for at least 2 hours prior to taking a dose to at least 1-hour post-dose for all doses. RXC004 is to be administered 30-60 minutes after administration of pembrolizumab.

[u] Triplicate ECGs should be collected as follows:
Cycle 0: CCI
Cycle 1, CCI
Cycle X, CCI
At selected sites, ambulatory Holter monitoring will be used on Cycle 0 Day 1 and Cycle 1 Day 15 for central analysis of digital ECG information.

[v] Follow-up assessments should be performed 30 days after discontinuation of RXC004 and 90 days after discontinuation of pembrolizumab.

[w] Thyroid panel should include: triiodothyronine (T3) or free T3, free thyroxine (T4), and thyroid stimulating hormone (TSH).

[x] Pembrolizumab 400 mg IV infusion over 30 minutes, q6w ± 3 days, unless an infusion needs to held due to an adverse event. Results for vital signs (including weight), performance status, chemistry, haematology, and thyroid function labs must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[y] CCI

[z] Screening pregnancy test to be performed in WOCPB within 72 h before start of study treatment. A positive pregnancy test within 72 h before study treatment initiation will result in exclusion from the study. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

CCI; C, Cycle; CT, computerised tomography; CCI; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; CCI; IP, investigational product; IV, intravenous; MRI, magnetic resonance imaging; CCI CCI; PD, pharmacodynamic(s); PD-L1, Programmed cell death ligand-1; PK, pharmacokinetic(s); q6w, every 6 weeks; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SC, subcutaneous; WOCBP, women of child-bearing potential.

12.10 Events of Clinical Interest for Pembrolizumab

Selected non-serious and serious AEs are also known as Events of Clinical Interest and must be reported to Redx Pharma within 24 hours of awareness.

Events of Clinical Interest for this study include:

1. An overdose of pembrolizumab, as defined in Section 8.4, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory test value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying aetiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying aetiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Medical Monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not Events of Clinical Interest for this trial.

12.11 Statistical Considerations

General statistical considerations can be found in Section 9.

12.11.1 Module 3 Sample Size Determination

The method by Frewer et al (Frewer et al 2016), together with the totality of the data collected, will be used to guide go/no-go decision making.

In the KEYNOTE-158 and KEYNOTE-028 studies, a combined response rate of approximately 10% 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 CCI CCI If response is seen in CCI or fewer patients, then there is less than a CCI% probability that the true ORR rate is greater than the CCI These hurdles will be used to guide

the decision for onward development. The totality of the data, including the population enrolled and the results from the secondary endpoints will be used for the final decision.

13 APPENDICES

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Redx will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with Redx.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests, which includes any changes to financial interests throughout and also after the study has concluded.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.

- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov, as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after the last marketing application unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 9 Publication Policy

- The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study centre will be set forth in the Clinical Trial Agreement.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support

publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e. run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs**.** If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is **not** the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g. neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a Redx study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet, tablet taken with food when it should be taken fasted.
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication
- Wrong drug administered to participant.

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

- Errors related to background and rescue medication, or standard of care medication in open-label studies.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Redx or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Redx-assigned biobanks or other sample archive facilities and will be tracked by the appropriate Redx Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, Redx is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to Redx or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Redx are informed about the sample disposal.

Redx ensures the organization(s) holding the samples is/are informed about the withdrawn consent as soon as reasonably possible and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are e.g., Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- Files would remain physically separate.

Appendix D RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) Responses

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have 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 smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
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.
New lesions	Always represents progressive disease (PD)

Appendix E Prohibited CYP3A4 Inhibitors and Inducers

CYP 3A4 Inhibitors **[Bold text denotes commonly used co-medications in patients with pancreatic or biliary tract cancers]**	**CYP 3A4 Inducers** **[None of these drugs are commonly used co-medications in patients with pancreatic or biliary tract cancers]**
Strong CYP 3A4 Inhibitors *Concomitant use of these drugs has the potential to increase the exposure of RXC004 >5-fold* *These agents must not be given within 14 days of first dose of study treatment* Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, **itraconazole, ketoconazole**, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), **posaconazole,** ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, **troleandomycin, voriconazole, clarithromycin,** idelalisib, **nefazodone,** nelfinavir.	**Strong CYP 3A4 Inducers** *Concomitant use of these drugs has the potential to decrease the exposure of RXC004 by >80%* *These agents must not be given within 14 days of first dose of study treatment* Aptalutimide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort.
Moderate CYP3A4 Inhibitors *Concomitant use of these drugs has the potential to increase the exposure of RXC004 by 2-5-fold* *A washout period of 14 days is recommended and a minimum washout period of 5 half-lives (See SMPC or USPI) is required before first dose of study treatment.* **Aprepitant,** , conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, **erythromycin, fluconazole, fluvoxamine,** imatinib, **tofisopam,** verapamil **lansoprazole.**	**Moderate CYP 3A4 Inducers** *Concomitant use of these drugs has the potential to decrease the exposure of RXC004 by 60-80%* *A washout period of 14 days is recommended and a minimum washout period of 5 half-lives (See SMPC or USPI) is required before first dose of study treatment.* Bosentan, efavirenz, etravirine, phenobarbital, primidone.
Weak CYP3A4 Inhibitors *These are not prohibited but should be used with caution as they may increase the exposure of RXC004 by 1.25 -2- fold* Chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor, omeprazole	**Weak CYP3A4 Inducers** *These drugs are not prohibited- they have the potential to decrease the exposure of RXC004 by 20-50% which is within the scope of the dose reduction allowances* Armodafinil, modafinil, rufinamide

For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Appendix F RNF43 Mutations (Module 1)

Module 1 will recruit patients with documented RNF43 mutated PDAC.

PDAC patients with the following RNF43 mutations are eligible for Module 1:

Patients with documented LoF RNF43 mutations other than those listed above may be allowed after consultation with Sponsor.

Appendix G Performance Status

G 1 Karnofsky Performance Status

Karnofsky performance status will be assessed for patients in Module 1 (PDAC) at the times specified in the Module 1 schedules of assessments based on the following:

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

G 2 ECOG Performance Status

ECOG performance status will be assessed for patients in Module 2 (BTC) at the times specified in the Module 2 schedule of assessments based on the following:

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

Appendix H Pharmacokinetic Parameter Definitions

PARAMETER	DEFINITION
C_{max}	The maximum observed concentration.
t_{max}	The time at which C_{max} was apparent.
AUC_{0-t}	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at t_{last} (the time of the last quantifiable concentration) calculated by the linear trapezoidal rule.
λ_z	The apparent terminal rate constant, estimated using the negative slope of the least square regression analysis of the log concentration versus time data for the terminal linear portion of the curve.
$t_{½}$	The apparent terminal half-life, calculated from $\log_e 2 / \lambda_z$.
$AUC_{0-\infty}$	The area under the concentration-time curve estimated from time zero to infinity as the sum of the two areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z.
CL	The systemic clearance calculated as: dose/ $AUC_{0-\infty}$.

Appendix I Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
AEPI	Adverse Event of Potential Interest
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BOR	Best Overall Response
BTC	Biliary tract cancer
CD8	Cluster of differentiation 8
C_{max}	Maximum (peak) observed plasma concentration
C_{min}	Minimum (trough) observed concentration across the dosing interval
CRO	Contract Research Organisation
CCA	Cholangiocarcinoma
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRC	Colorectal cancer
CrCL	Creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CCI	CCI
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DBL	Data Base Lock
DCO	Data Cut Off
DCR	Disease Control Rate
DILI	Drug-induced liver injury
CCI	CCI
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
EU	European Union

Abbreviation or special term	Explanation
eCRF	electronic Case Report Form
FDA	U.S. Food and Drug Administration
CCI	CCI
FFPE	Formalin-fixed, paraffin-embedded
Fz	Frizzled
GCP	Good Clinical Practice
HBV	Hepatitis B
HCV	Hepatitis C
IB	Investigator's Brochure
ICF	Informed Consent Form
IP	Investigational Product
irAE	Immune-related adverse event
IV	Intravenous
LoF	Loss of function
LRP	Low-density lipoprotein receptor-related protein
ORR	Overall Response Rate
OS	Overall survival
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein-1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PORCN	Porcupine
PR	Partial response
QD	Once daily
q[x]w	Every [x] weeks
RECIST	Response Evaluation Criteria In Solid Tumours
RNF43	Ring finger protein 43
RSPO	R-Spondin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease

Abbreviation or special term	Explanation
SMC	Safety monitoring committee
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SoC	Standard of Care
SRC	Safety review committee [for the Phase 1 study]
Treg	Regulatory T-cell

Appendix J Dysgeusia Treatment Guidelines

As there are no recognised standard international guidelines for the management of this multifactorial event, investigators are advised to consult their local practice guidelines for the management of dysgeusia. Please refer to Table 11, Section 6.5 for instructions on dose reductions and interruptions for dysgeusia.

Some interventions may be effective in treating dysgeusia:

- Treatment with oral pilocarpine and artificial saliva may help in cases where there is also dry mouth
- Zinc supplements may help in cases where there is evidence of zinc deficiency
- Alpha lipoic acid is an antioxidant capsule supplement which may improve flavour sensation
- Good oral hygiene and chlorhexidine (or similar) mouthwashes

Patients may be advised of some ways that they can manage dysgeusia, for example:

- Cooking or eating food in non-metallic cookware
- Avoiding foods that taste bitter or metallic
- Flavoring foods with seasonings and spices
- Eating food cold may help to reduce unpleasant flavor sensations
- Frequently brushing teeth
- Rinsing with mouth wash regularly
- Using chewing gum. Lozenges or mints to stimulate saliva production

A dysgeusia treatment algorithm has been developed by Sevryugin et al 2021 based on their review of published studies of dysgeusia interventions and is included to assist Investigators with the management of dysgeusia that occurs during treatment with RXC004. However, it is acknowledged that not all of the management suggestions may be readily available or applicable to patients in this study.

Figure 2 Dysgeusia Treatment

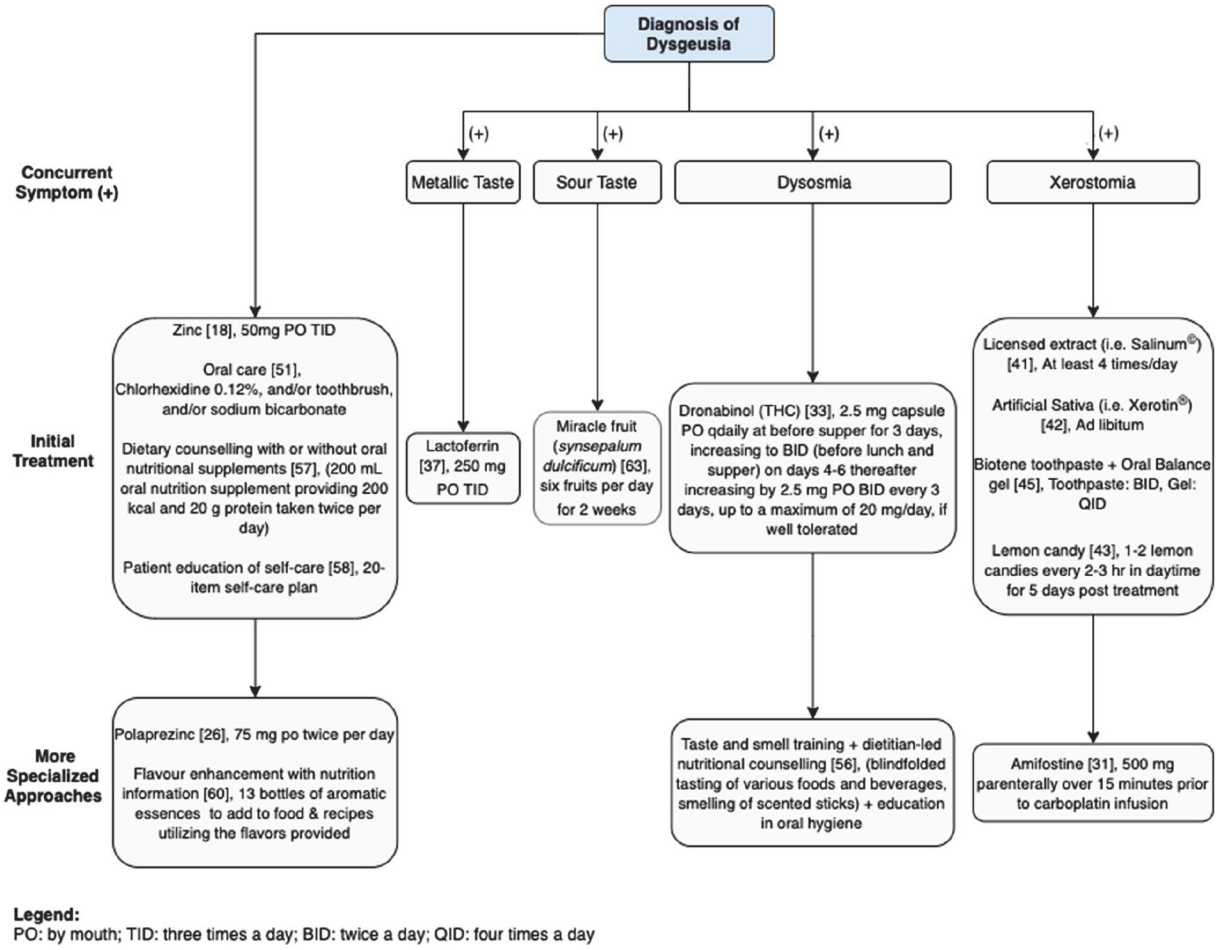


Figure from Sevryugin et al 2021.

Appendix K Management of Colitis Events

In the Phase 1 study of RXC004, events of colitis or enteritis were reported in four patients who commenced treatment at doses of 3 mg QD or 10 mg QD. At the time of publishing this protocol, an SAE of Grade 3 enteritis has been reported in 1 patient out of 12 patients dosed in the Phase 2 study RXC004/0002 and an SAE of Grade 3 colitis has been reported in 1 patient out of 21 patients dosed in this Phase 2 study (RXC004/0003). Both patients were receiving RXC004 2 mg QD. The enteritis and the colitis events were both considered by the Investigator as RXC004-related.

RXC004-related diarrhoea/colitis may present as abdominal pain with other symptoms including intermittent constipation, diarrhoea, nausea and/or vomiting. In some cases, symptoms may be minimal. Blood and mucus in the stool may not be apparent. Symptoms may be preceded by or accompanied by a raised CRP and neutrophil count.

Pembrolizumab is also known to cause irAEs including colitis.

If lower GI-tract inflammation is suspected, infectious and other causes should be excluded, including CMV and *C. difficile*. Attempts should be made to definitively diagnose the condition with a CT scan and colonoscopy/sigmoidoscopy with biopsy, if clinically safe to do so.

Management:

Monitoring of CRP or fecal calprotectin levels may help to monitor the response to treatment.

Table 19 Management of Colitis Events

Event and grade	Management
Grade 1 colitis (asymptomatic but evidence on CT scan)	Continue RXC004 at a lower dose and repeat the CT scan within 4 weeks. No action is needed for pembrolizumab. No additional treatment is indicated. If the Grade 1 colitis is evident on- the second scan despite the lower dose of RXC004, it should be managed as Grade 2 colitis and the scan should be repeated within 4 weeks.
Grade 2 colitis (abdominal pain, mucus or blood in stool)	Pause RXC004 and pembrolizumab (if applicable).

Event and grade	Management
	Manage with corticosteroids at a dose of 1-2 mg mg/kg methylprednisolone equivalent. When symptoms have resolved, taper over 2-4 weeks. If symptoms recur during tapering, the steroid dose may need to be increased again. If no improvement in 72 hrs despite treatment, treat as Grade 3. RXC004 can be restarted at a lower dose after colitis has resolved to Grade ≤ 1* and steroids tapered to physiological levels (<10 mg prednisolone per day equivalent dose) over at least 1 month. If steroids cannot be tapered to physiological levels within 12 weeks of commencing steroid treatment, then RXC004 and pembrolizumab (if applicable) should be permanently discontinued.
Grade 3 colitis (severe or persistent abdominal pain, fever, ileus; peritoneal signs)	Pause RXC004 and pembrolizumab, if applicable. Seek specialist advice. Manage with corticosteroids at a dose of 1-2 mg/kg methlyprednisolone equivalent. When symptoms improve, taper steroids to physiological levels over 4-8 weeks and consider use of prophylactic antibiotics and anti-fungals. RXC004 can be restarted at a lower dose after colitis has resolved to Grade ≤ 1* and steroids tapered to physiological levels

Event and grade	Management
	(<10 mg prednisolone per day equivalent dose) If steroids cannot be tapered to physiological levels within 12 weeks of commencing steroid treatment, then RXC004 and pembrolizumab, if applicable, should be permanently discontinued Additional anti-inflammatory medications (e.g. infliximab) may be indicated if no improvement in 48-72 hrs. **It is important to rule out bowel perforation and refer to infliximab SMPC/USPI for general guidance before using infliximab.** If anti-inflammatories are required RXC004 and pembrolizumab, if applicable, should be permanently discontinued.
Grade 4 colitis (life-threatening consequences)	Manage as Grade 3 colitis. **RXC004 and pembrolizumab, if applicable, should be permanently discontinued.**

*Attempts should be made to confirm that the colitis has resolved to Grade ≤ 1 (e.g. normalised CRP or fecal calprotectin if raised during event; GI appearance normalised on X ray/ CT or endoscopy) before restarting RXC004.

If there is any recurrence of colitis ≥ Grade 2 after recommencing RXC004, **RXC004 and pembrolizumab, if applicable, should be permanently discontinued.**

Appendix L Pembrolizumab Dose Modification and Toxicity Management

L 1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunological aetiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 20.

Table 20 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:	1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhoea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus) Participants with ≥ Grade 2 diarrhoea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycaemia	New onset T1DM or	Type 1 diabetes mellitus (T1DM) or hyperglycaemia	Initiate insulin replacement therapy for participants with T1DM Administer antihyperglycemic in participants with hyperglycaemia	Monitor participants for hyperglycaemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 2, 3, or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm aetiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold		

Immune-related AEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3	Withhold or discontinue based on the event [e]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm aetiology or exclude other causes
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: > 3.0 to 5.0× ULN if baseline normal; >3.0 to 5.0× baseline, if baseline abnormal; bilirubin:> 1.5 to 3.0× ULN if baseline normal; > 1.5 to 3.0× baseline if baseline abnormal.

[b] AST/ALT: >5.0 to 20.0× ULN, if baseline normal; >5.0 to 20.0× baseline, if baseline abnormal; bilirubin:> 3.0 to 10.0× ULN if baseline normal; > 3.0 to 10.0× baseline if baseline abnormal

[c] AST/ALT: >20.0× ULN, if baseline normal; >20.0× baseline, if baseline abnormal; bilirubin: > 10.0× ULN if baseline normal; >10.0× baseline if baseline abnormal.

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

AE(s), adverse event(s); ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, Drug Rash with Eosinophilia and Systemic Symptom; GI, gastrointestinal; IO, immune-oncology; ir, immune related; IV, intravenous; SJS, Stevens-Johnson Syndrome; T1DM, type 1 diabetes mellitus; TEN, Toxic Epidermal Necrolysis; ULN, upper limit of normal.

L 2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 21.

Table 21 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine) Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grade 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalisation may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.
IV, intravenous; NSAID, non-steroidal anti-inflammatory drug.

L 3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, pembrolizumab is to be restarted within 6 weeks or 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the patient's study record.

Appendix M Protocol Amendment History

Version 5.0 – 19 August 2022

Substantial changes:

Incorporation of a lower RXC004 dose cohort within Module 2, for the evaluation of RXC004 1 mg monotherapy in patients with biliary tract cancer:

Sections updated: Synopsis (1.1), Sections 2.1, 4.1, 4.4.1, 6.1, 11.5, 11.8.1, and 11.9.1.

New sections added: Sections 4.4.1.6.

Incorporation of an additional Module (Module 3) and supporting data to evaluate the combination of RXC004 1.5 mg with pembrolizumab in patients with biliary tract cancer:

Sections updated: Synopsis (1.1), Sections 2.1, 2.2.2, 2.2.3, 2.3.1, 3, 4.1, 4.3, 4.4.1, 5.3, 6.1, 6.5, 6.6, 7.1, 8.2.1, 8.2.6, 8.3.1, 8.3.2, 8.4, 8.6.1.1, 9.1, 9.3, 9.4.2.1, 9.4.3.1, 9.6, and Appendix K.

New sections added: 2.2.4, 2.3.3, 2.3.4, 4.4.1.2, 4.4.1.7, 5.5, 6.2.3, 6.3.2, 6.4.1, and 12.

Clarification of prophylactic treatment regimens with denosumab and calcium:

Sections updated: Sections 2.3.1.2, 6.2.2, 10.8.1.

Clarification of timings for baseline biopsy and baseline CCI

Sections updated: Sections 10.8.1, 11.8.1.

Clarification of inclusion criteria and concomitant treatments relating to prior anticancer therapy and the time window allowed between radiologically confirmed progression and start of study treatment:

Sections updated: Section 5.2, 5.3, 5.4, 5.6.3.

Clarification of DEXA scans at screening for patients with osteoporosis:

Sections updated: Section 5.4, 10.8.1, 11.8.1.

Update to guidance on prohibited CYP3A4 inhibitors and inducers:

Sections updated: 5.6.3.1, Appendix E.

Update to RXC004 dose modification guidance:

Section updated: Section 6.5.

Non-substantial changes:

Clarification of pre-screening genetic testing: Section 5.8.

At selected sites, digital ECG collection may take place using ambulatory Holter monitoring equipment on Cycle 0 Day 1, and Cycle 1 Day 15: Sections 8.2.4, 10.8.1, 11.8.1. Appendices grouped under an overall Section header: Section 13. Updates and corrections to Abbreviations and References: Appendix I and Section 14, respectively. Protocol amendment history moved to an Appendix: Appendix L.
Version 4.0 – 17th November 2021
1. The following updates were made to the eligibility criteria: a. Exclusion criteria updated to exclude patients with QTcF >470 ms, for consistency with sister study RXC004/0002 (NCT04907539). b. Creatinine clearance inclusion criteria and monitoring added to enable future population PK analysis of effect of CLcr on PK of RXC004, for consistency with sister study RXC004/0002 (NCT04907539). c. Exclusion criteria #12 updated for clarity **Sections updated - Section 5.1, Section 5.4, Table 10 and Table 11** 2. Guidelines for management of colitis events updated after IB updated. Dose modification tables, prohibited medications and safety labs also updated accordingly. **Sections updated – Section 5.5.3, Section 6.5, Table 6 and Appendix K.** 3. RXC004 background, benefit-risk assessment and dose justification updated to include data from the most recent IB. **Sections updated- Section 2.2.3, Section 2.3.1, Section 10.3.2, Section 11.3.2 and Section 4.4.** 4. AEs of potential interest (AEPI) identified for monitoring: bone toxicities and colitis events. **Section added – Section 8.3.14.** 5. Contraception requirements updated to include the definition of sexual abstinence, per MHRA request. **Section updated – Section 5.5.1.** 6. Clarification for treating patients after RECIST1.1 progression added. **Sections updated 7.1.1.** 7. Restrictions on the use of concomitant CYP3A4 inhibitors and inducers updated to include 2 weeks prior to first dose of study treatment, for consistency with sister study RXC004/0002 (NCT04907539). **Section updated – Section 5.5.3.** 8. Maximum 14 days' RXC004 interruption without Sponsor approval - language removed from protocol as a clarification for situations where it conflicts with advice for management of colitis in Appendix K. **Section updated - Section 6.5.** 9. RXC004 fasting requirements from Section 5.5.2 added to schedule of assessment footnotes and

RXC004 handling instructions for clarity. **Sections updated – Table 10, Table 11 and Section 6.2.1.**

10. CCI [redacted]

11. Dysgeusia management and dose modification guidelines updated for clarity. **Sections updated – Table 6 and Appendix J.**

12. CCI [redacted]

13. ECG monitoring plan revised to include monitoring around the anticipated maximal RXC004 concentration on Cycle 0 Day 1 (first dose) and Cycle 1 Day 15 (steady state) and retention of ECG traces added as part of a programme initiative to enable future QT investigations if required. **Section updated – Section 8.2.4, Table 10 and Table 11**

14. CCI [redacted] assessments changed from optional to mandatory unless unavailable at site to clarify the original intention that these assessments should be performed if the site has the capability to do so. **Section Updated – Section 8.6.3, Table 10 and Table 11**

15. Minor editorial changes were made throughout the protocol for consistency and clarity.

Version 3.0 – 19th June 2021

1. Dose of RXC004 used in both Module 1 and 2 updated to 2mg QD, due to recent data from Phase 1 study and Safety Review Committee recommendations. RXC004 background, risk/benefit, dose rationale and dose modification sections also updated with most recent data from the Phase 1 dose escalation study. **Sections updated – Section 2.2.3, Section 2.3.1, Section 4.4.1, Table 1, Table 2, Table 3, Table 4, Table 7 and Table 8**

2. A pre-screening period to identify RNF43 loss of function mutations from a centralised panel CCI [redacted] has been added to Module 1. Module 1 specific inclusion criteria has also been amended accordingly. **Sections updated – Figure 1, Section 5.2, Table 7 and Section 8.6.1.1**

3. Acceptable methods of contraception in the lifestyle consideration updated to be consistent with the Clinical Trial Facilitation Group (CTFG) recommendations for highly effective methods of contraception. **Sections updated – Section 5.5.1**

4. Management plan for RXC004 related diarrhoea/colitis events added after safety review of data from the Phase 1 study. **Sections added – Appendix K**

5. Assessments to characterise and guidelines to treat RXC004 related dysgeusia added to protocol. Assessment of dysgeusia also added to Secondary safety objective. **Sections updated – Section 8.3.12, Table 7, Table 8, Section 3 and Appendix J**

6. CCI [redacted]

CCI [redacted]
CCI [redacted]
CCI [redacted] **Sections updated – Section 3, Table 7 and Section 5.7**

7. The following items have been added to the protocol as a result of the COVID-19 vaccination risk assessment:

    a. receipt of live (capable of replication) vaccinations within 4 weeks of starting study treatment and during study treatment added to exclusion criteria and prohibited medications. **Sections updated – Section 5.4 and Section 5.5.3.1**

    b. Clarification on permitted COVID-19 vaccinations. **Sections updated – Section 5.5.3.1 and 5.5.3.2**

    c. Interruption of RXC004 for COVID-19 infections added to dose interruption and stopping criteria. **Sections updated – Table 3**

    d. Clarification on collection of COVID-19 adverse events added**. Sections updated – Section 8.3.11**

8. Details of a Safety Monitoring Committee for Redx Phase 2 RCX004 studies added to protocol. **Sections updated – Section 9.6**

9. Inconsistencies in the scheduling of various assessments between Module 1 and Module 2 corrected. **Sections updated – Table 7 and Table 8**

10. Permitted windows added to pharmacokinetic sample timepoints on Cycle 0 Day 1 and Cycle 1 Day 15. **Sections updated – Table 7 and Table 8**

11. Collection of fresh blood for PD analysis after Cycle 2 removed, based on emerging data from Phase 1 study which indicates that collection of samples after Cycle 2 is not required. **Sections updated – Table 7 and Table 8**

12. Minor editorial changes were made throughout the protocol for consistency and clarity

Version 2.0 – 09 March 2021

1. CCI [redacted] pre-screening period removed and Module 1 specific inclusion criterion #8 amended to clarify that eligible patients must have documented evidence of a CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted], in response to MHRA feedback. **Sections updated – Figure 1, Section 5.1, Section 5.2, Section 8.6.1, Section 10.5 and Table 7.**

2. Duration of contraception for women of childbearing potential amended to take into account the requirements for patients using denosumab, as per MHRA request. **Sections updated - Section 5.1, 5.5.1 and 8.3.10**.

3. Lifestyle restrictions updated to include avoiding direct sunlight and use of tanning equipment, as per

MHRA request. **Section updated - Section 5.5 (new Section 5.5.4 added)** 4. Schedule of assessments and time period for collection of adverse events clarified to be from signature of the main study informed consent, as per MHRA request. **Sections updated - Section 8.3.1, Table 7 and Table 8** 5. Reference to Nivolumab removed from Section 8.3.9, as per MHRA request. **Section updated – Section 8.3.9.**
Version 1.0 – 14 December 2020
Initial creation

14 REFERENCES

Abou-Alfa et al 2020
Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671-684.

Bailey et al 2016
Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al; Australian Pancreatic Cancer Genome Initiative. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47-52.

Blank et al 2004
Blank C, Brown I, Peterson AC, Siotto M, Iwai Y, Honjo T, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004;64(3):1140-5.

Burris et al 1997
Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6): 2403-13.

Boulter et al 2015
Boulter L, Guest RV, Kendall TJ, Wilson DH, Wojtacha D, Robson AJ, et al. WNT signaling drives cholangiocarcinoma growth and can be pharmacologically inhibited. J Clin Invest. 2015;125(3):1269-1285.

Cerami et al 2012
Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-404.

Chemnitz et al 2004
Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004,173(2):945–954.

Citterio et al 2018
Citterio C, Baccini M, Orlandi E, Di Nunzio C, Cavanna L. Second-line chemotherapy for the treatment of metastatic pancreatic cancer after first-line gemcitabine-based chemotherapy: a network meta-analysis. Oncotarget. 2018;9(51):29801-29809.

Conroy et al 2011
Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al, Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX Versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med. 2011;364(19):1817-1825.

Cook et al 2021
Cook N, Blagden S, Lopez J, Sarker D, Greystoke A, Harris N, et al. 517MO - Phase I study of the porcupine (PORCN) inhibitor RXC004 in patients with advanced solid tumours. Ann Oncol. 2021;32(Suppl_5):S583-S620.

Curran et al 2010
Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A. 2010;107(9):4275-80.

Disis 2010
Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28(29):4531-4538.

Dudley et al 2005
Dudley ME, Wunderlich JE, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23(10):2346-57.

Francisco et al 2010
Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42.

Frewer et al 2016
Frewer P, Mitchell P, Watkins C, Matchman J. Decision-making in early clinical drug development. Pharmaceutical Statistics. 2016;15:255-263.

Goldsberry et al 2019
Goldsberry WN, Londoño A, Randall TD, Norian LA, Arend RC. A Review of the Role of Wnt in Cancer Immunomodulation. Cancers. 2019;11(6):E771.

Greenwald et al 2005
Greenwald RJ, Freeman GJ, Sharpe AH. The B7 Family Revisited. Annu Rev Immunol. 2005;23:515–48.

Haanen et al 2017
Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al, on behalf of the ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl_4):iv119-iv142.

Hao et al 2016
Hao HX, Jiang X, Cong F. Control of Wnt Receptor Turnover by R-spondin-ZNRF3/RNF43 Signaling Module and Its Dysregulation in Cancer. Cancers (Basel). 2016;8(6):54.

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65(3):1089-96.

Hunder et al 2008
Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med. 2008;358(25):2698-703.

Janku et al 2015
Janku F Connolly R, LoRusso P, de Jonge M, Vaishampayan U, Rodon J, et al. Abstract C45: Phase I study of WNT974, a first-in-class Porcupine inhibitor, in advanced solid tumors. Mol Cancer Ther. 2015;14(12 Supplement 2):p.C45.

Janku et al 2020
Janku F, de Vos F, de Miguel M, Forde P, Ribas A, Nagasaka M, et al. Abstract CT034: Phase I study of WNT974 + spartalizumab in patients (pts) with advanced solid tumors. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27-28 and Jun 22-24. Philadelphia (PA): AACR; Cancer Res. 2020;80(16_Suppl):CT034.

Jiang et al 2013
Jiang X, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, et al. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. Proc Natl Acad Sci USA. 2013;110(31):12649-12654.

KEYTRUDA SmPC
Summary of Product Characteristics. KEYTRUDA 25 mg/mL concentrate for solution for infusion. Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed 16 May 2022.

Kleeman et al 2020
Kleeman SO, Koelzer VH, Jones HJ, Vazquez EG, Davis H, East JE, et al. Exploiting

differential Wnt target gene expression to generate a molecular biomarker for colorectal cancer stratification. Gut. 2020;69(6):1092-1103.

Koo et al 2015
Koo BK, van Es JH, van den Born M, Clevers H. Porcupine Inhibitor Suppresses Paracrine Wnt-driven Growth of Rnf43;Znrf3-mutant Neoplasia. Proc Natl Acad Sci. USA. 2015;112(24):7548-7550.

Lala et al 2020
Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020;131:68-75.

Lamarca et al 2019
Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC + mFOLFOX) for patients with locally advanced/metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. J Clin Oncol. 2019;37(15_suppl):4003-4003.

Levit et al 2019
Levit L, Peppercorn, J, Tam A, Marron J, Mathews D, Levit K, et al. Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement. J Clin Oncol. 2019, 37:2368-2377.

Loilome et al 2014
Loilome W, Bungkanjana P, Techasen A, Namwat N, Yongvanit P, Puapairoj A, et al. Activated macrophages promote Wnt/β-catenin signaling in cholangiocarcinoma cells. Tumour Biol. 2014;35(6):5357-5367.

Luke et al 2019
Luke JJ, Bao R, Sweis RF, Spranger S, Gajewski TF. WNT/β-catenin Pathway Activation Correlates with Immune Exclusion across Human Cancers. Clin. Cancer Res. 2019;25(10):3074-3083.

Madan et al 2016
Madan B, Ke Z, Harmston N, Ho SY, Frois AO, Alam J, et al. Wnt Addiction of Genetically Defined Cancers Reversed by PORCN Inhibition. Oncogene. 2016;35(17):2197-2207.

Makena et al 2019
Makena MR, Gatla H, Verlekar D, Sukhavasi S, Pandey MK, C Pramanik CK. Wnt/β-Catenin Signaling: The Culprit in Pancreatic Carcinogenesis and Therapeutic Resistance. Int J Mol Sci. 2019;20(17):4242.

Matsumoto et al 2020
Matsumoto A, Shimada Y, Nakano M, Oyanagi H, Tajima Y, Nakano M, et al. RNF43 Mutation Is Associated With Aggressive Tumor Biology Along With BRAF V600E Mutation in Right-Sided Colorectal Cancer. Oncol Rep. 2020;43(6):1853-1862.

Murillo-Garzon and Kypta 2017
Murillo-Garzón V, Kypta R. WNT signalling in prostate cancer. Nat Rev Urol. 2017;14(11):683-696.

Ng et al 2017
Ng M, Tan DSP, Subbiah V, Weekes CD, Teneggi V, Diermayr V, et al. First-in-human phase 1 study of ETC-159 an oral PORCN inhibitor in patients with advanced solid tumours. J Clin Oncol. 2017;35(15_suppl):2584-2584.

Noll et al 2016
Noll AT, Cramer T, Olde Damink SW, Schaap FG. Cholangiocarcinoma, gone without the Wnt? World J Hepatol. 2016;8(26):1093-1096.

Nomi et al 2007
Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13(7):2151-7.

Oh et al 2022
Oh DY, He AR, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid. 2022;1(8).

Okazaki et al 2001
Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A. 2001;98(24):13866-71.

Parry et al 2005
Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 2005;25(21):9543-53.

Pelzer et al 2011
Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011;47(11):1676-81.

Piha-Paul et al 2020
Piha-Paul SA, Oh DY, Ueno M, Malka D, Chung HC, Nagrial A, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer. 2020;147:2190-2198.

Pilon-Thomas et al 2010
Pilon-Thomas S, Mackay A, Vohra N, Mulé JJ. Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol. 2010;184(7):3442-9.

Primrose et al 2019
Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al, BILCAP study group. Capecitabine Compared With Observation in Resected Biliary Tract Cancer (BILCAP): A Randomised, Controlled, Multicentre, Phase 3 Study. Lancet Oncol. 2019;20(5):663-673.

Riley 2009
Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229(1):114-25.

Rodon et al 2021
Rodon J, Argiles G, Connolly RM, Vaishampayan U, de Jonge M, Garralda E, et al. Phase 1 study of single-agent WNT974, a first-in-class Porcupine inhibitor, in patients with advanced solid tumours. Brit J Cancer. 2021;125(1):28-37.

Sevryugin et al 2021
Sevryugin O, Kasvis P, Vigano ML, Vigano A. Taste and smell disturbances in cancer patients: a scoping review of available treatments. Support Care Cancer. 2021;29:49-66.

Sheppard et al 2004
Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 ζ signalosome and downstream signaling to PKCθ. FEBS Lett. 2004;574(1-3):37-41.

Siegel et al 2020
Siegel RL, Miller KD, Jemal A. Cancer statistics 2020. CA Cancer J Clin. 2020;70:7-30.

Spranger et al 2014
Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer. 2014;2:3.

Spranger and Gajewski 2018
Spranger S and Gajewski TF. Impact of oncogenic pathways on evasion of antitumour immune responses. Nat Rev Cancer. 2018;18(3):139-147.

Strome et al 2003
Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003;63(19):6501-5.

Thibodeau and Voutsadakis 2018
Thibodeau S, Voutsadakis IA. FOLFIRINOX Chemotherapy in Metastatic Pancreatic Cancer: A Systematic Review and Meta-Analysis of Retrospective and Phase II Studies. J Clin Med. 2018;7(1):7.

Valle et al 2010
Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-1281.

Valle et al 2020
Valle JW, Bai LY, Orlova R, Van Cutsem E, Alfonso J, Chen A, et al. Ramucirumab (RAM) or merestinib (MER) or placebo (PL) plus gemcitabine (GEM) and cisplatin (CIS) as first-line treatment for advanced or metastatic biliary tract cancer (BTC): A randomized, double-blind, phase II study. J Clin Oncol. 2020;38(4_suppl):abstract 477.

Vodicka et al 2020
Vodicka P, Krskova L, Odintsov I, Krizova L, Sedlackova E, Schutzner J, Zamecnik J. Expression of molecules of the Wnt pathway and of E-cadherin in the etiopathogenesis of human thymomas. Oncol Lett. 2020;19(3):2413-2421.

Von Hoff et al 2011
Von Hoff D, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: A Phase I/II trial. J Clin Oncol. 2011;29(34):4548-4554.

Waddell et al 2015
Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P; Australian Pancreatic Cancer Genome Initiative, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495-501.

Wang et al 2018
Wang B, Tian T, Kalland KH, Ke X, Qu Y. Targeting Wnt/beta-Catenin Signaling for Cancer Immunotherapy. Trends Pharmacol Sci. 2018;39(7);648-658.

Wang-Gillam et al 2016
Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised,

open-label, phase 3 trial. Lancet. 2016;387(10018):545-557.

Weber 2010
Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol. 2010;37(5):430-9.

Zhan et al 2016
Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene. 2016;36(11):1461-1473.

Zhang et al 2004
Zhang X, Schwartz JCD, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20(3):337-347. Erratum in Immunity. 2004 May;20(5):651.