CLINICAL STUDY PROTOCOL

PRISM-1

A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 3 Trial of Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients With Treatment-Naive Metastatic Pancreatic Ductal Adenocarcinoma

Short Title:

Randomized Phase 3 Trial of Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients With Metastatic Pancreatic Ductal Adenocarcinoma

Investigational Product(s)	Quemliclustat (AB680)
Protocol Number	PRISM-1
Clinical Phase	Phase 3
Sponsor	Arcus Biosciences, Inc. (Arcus) 3928 Point Eden Way Hayward, CA 94545
Regulatory Agency Identifier Number(s)	IND: 141356 CTIS: 2024-513317-12-00
Protocol Version; Date of Approval	Version 1.0/NA-1; 02 December 2024
Global Protocol Version; Date of Approval	Version 1.0; 03 July 2024

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6 (R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential patients.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled patients may be necessary depending on the nature of the amendment.

The principal investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study patients.

All personnel involved in the conduct of this study have completed Human Research Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 3 Trial of Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients With Treatment-Naive Metastatic Pancreatic Ductal Adenocarcinoma
Protocol Number	PRISM-1

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature below.

Name:	**Title:**
Signature: *See appended signature page*	**Date:** [DD-Month-YYYY]

A separate signature page denoting approval will be generated and placed at the end of the protocol.

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study PRISM-1 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6 (R2).
- To obtain approval for the protocol and all written materials provided to patients prior to initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those patients.
- To maintain participation records and all required protocol data for each patient.

Name:	**Title:**	**Institution:**
Signature:		**Date:**

STUDY CONTACT INFORMATION

Table 1: Study Contact Information

Role in Study	Email Address
Medical Monitor	medicalmonitor-prism-1@arcusbio.com

DOCUMENT HISTORY

Amendment	Issue Date
Global Protocol V1.0	03 July 2024

AMENDMENT SUMMARY

This PRISM-1 Protocol Version 1.0/North America (NA)-1 replaces PRISM-1 Protocol Version 1.0. This amendment is considered 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.

The primary purpose of Version 1.0/NA-1 is to permit the use of generic or any brand of nab-paclitaxel that is approved for this indication in the country of randomization, as per standard of care practice. This improves access to this study to potential patients by removing the restriction of brand name Abraxane® or Pazenir® only. The updates from protocol administrative letter #1 are also included. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Section Number and Name	Summary of Change	Rationale for Change
Global Administrative Updates	The document versioning was updated to reflect current amendment. Grammar, sentence structure, clarity, and style updates were made as necessary. Document History and Amendment Summary Headings added.	Updates were made to align with the current Arcus Style Guide. New sections added per Arcus Style and formatting for Amendments.
Study Contact Information and Section 10.4.8 – Serious Adverse Event Reporting Requirements	Medical Monitor name was removed.	Updated to reflect Arcus processes.
Section 5.2 – Study Design and Schedule of Assessments	Figure 1 was updated to correct an administrative error.	Update was made for clarity.
Section 6.2 – Inclusion Criteria	Inclusion 8 and 9 laboratory values prior to days prior to randomization was updated from ≤ 14 days to ≤ 7 days to align with the Schedule of Assessments.	Administrative error was corrected.
Section 7.1 – Study Treatments Administered	Language was added to the section and Table 6 to allow for generic nab-paclitaxel.	Language was added to provide flexibility.
Appendix 1 – Toxicity Management Guidelines for Quemliclustat	Hepatitis/transaminitis, endocrinopathies, nephritis, diarrhea/colitis, pneumonitis, and pancreatitis guidance updated.	Updates were made to reflect changes in protocol administrative letter #1.

1. SYNOPSIS

Name of Sponsor	Arcus Biosciences, Inc.
Protocol Number	PRISM-1
Title	A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 3 Trial of Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients With Treatment-Naive Metastatic Pancreatic Ductal Adenocarcinoma
Short Title	Randomized Phase 3 Trial of Quemliclustat and Chemotherapy Versus Placebo and Chemotherapy in Patients With Metastatic Pancreatic Ductal Adenocarcinoma
Regulatory Agency Identifier(s)	IND: 141356 CTIS: 2024-513317-12-00
Name of Investigational Product	Quemliclustat (AB680)
Study Drugs	Quemliclustat (AB680) Nab-paclitaxel (NP) and gemcitabine (Gem) (NP-Gem)
Study Phase	Phase 3
Number of Study Centers	Up to approximately 200 sites globally
Target Population	Patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)
Number of Patients	Approximately 610 patients
Study Design	This is a randomized, placebo-controlled, double-blind, 2-arm, global, multicenter, Phase 3 study to evaluate the overall survival (OS) of quemliclustat versus placebo when each is given in combination with standard-of-care (SOC) NP-Gem in patients with confirmed mPDAC previously untreated in the metastatic setting. Approximately 610 patients will be enrolled in the study and randomized 2:1 to Arm A or Arm B. Patient randomization will be stratified by presence or absence of liver metastases; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 versus 1); and region (North America and Western Europe versus East Asia versus Rest of World). A patient is considered enrolled after completing the informed consent process, meeting all eligibility criteria, none of the exclusion criteria, and being randomized. **Arm A (Experimental Arm)** Doses and administration of quemliclustat, NP, and Gem will be administered using a 28-day cycle: • Quemliclustat administered at 100 mg intravenously (IV) over 30 minutes (± 5 minutes) on Days 1 and 15 of each cycle • Nab-paclitaxel administered at 125 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle • Gemcitabine administered at 1000 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle

	Arm B (Comparator Arm) Doses and administration of placebo, NP, and Gem will be administered using a 28-day cycle: • Placebo administered every 2 weeks IV over 30 minutes (± 5 minutes) on Days 1 and 15 of each cycle • Nab-paclitaxel administered at 125 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle • Gemcitabine administered at 1000 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle Crossover between the experimental and comparator arms is not allowed. Patients should continue treatment until permanent treatment discontinuation criteria are met. In addition, the maximum treatment duration for quemliclustat/placebo is 2 years from the initial dose. An independent data monitoring committee (IDMC) will be used in this study to monitor the ongoing safety of the investigational product in patients as well as at the prespecified interim efficacy analysis, as described in the IDMC Charter. Patients will complete 4 study periods: Screening (up to 28 days prior to Cycle 1, Day 1), Treatment, Safety Follow-Up (SFU), and Long-Term Follow-Up (LTFU). Safety measures will be assessed at regular intervals throughout the duration of treatment and during the 30-day SFU period. Disease assessments will be performed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) every 8 weeks through Cycle 12 then every 12 weeks thereafter, regardless of treatment delays. Treatment beyond initial radiographic disease progression (in the absence of clear clinical deterioration) is permitted at the discretion of the investigator, based on the perceived benefit-risk profile of an individual patient, until a second radiographic disease progression per RECIST v1.1 occurs. If radiographic disease progression is confirmed by the investigator per RECIST v1.1 at the next scheduled disease assessment no sooner than 4 weeks from the previous assessment of radiographic progressive disease, treatment must be permanently discontinued. Pharmacokinetic parameters, exploratory biomarkers, and patient-reported outcomes will also be assessed.
Rationale	This study is designed as a randomized, placebo-controlled, double-blind, 2-arm, global, multicenter, Phase 3 study in adult patients with treatment-naive mPDAC. Based upon the OS data reported from Study ARC-8 for the combination of quemliclustat and NP-Gem in first-line mPDAC, it is hypothesized that the addition of quemliclustat to NP-Gem will clinically meaningfully and significantly improve OS compared to placebo and NP-Gem. Nab-paclitaxel in combination with Gem is broadly approved globally and recommended by various regional compendiums, such as National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology, as a SOC for patients with first-line mPDAC. Accordingly, NP-Gem has been chosen as the SOC option to combine with quemliclustat in the experimental arm and will therefore serve as the comparator when given in combination with placebo.
Data Monitoring Committee/Other Committee	Yes

Study Objectives, Endpoints	Objectives	Endpoints
Primary	• To compare OS of quemliclustat + NP-Gem versus placebo + NP-Gem in all randomized patients.	• Overall survival is defined as the time from date of randomization until the date of death from any cause.
Secondary	• To compare progression-free survival (PFS) of quemliclustat + NP-Gem versus placebo + NP-Gem in all randomized patients.	• Progression-free survival is defined as the time from the date of randomization until disease progression or death from any cause, whichever comes first, as measured per RECIST v1.1 as assessed by the investigator.
	• To assess additional measures of clinical activity in all randomized patients.	• Objective response rate (ORR) is defined as the proportion of patients who have achieved best overall response of confirmed complete response (CR) or partial response (PR) to study therapy as assessed by the investigator according to RECIST v1.1. • Duration of response is defined as the time from the first objective response (CR or PR) until the date of first documented disease progression or death, whichever comes first, as measured per RECIST v1.1 as assessed by the investigator. • Disease control rate is defined as the proportion of patients who have achieved confirmed CR, confirmed PR, or stable disease for ≥ 8 weeks from the date of randomization, as assessed by the investigator according to RECIST v1.1.
	• To assess the safety and tolerability of quemliclustat or placebo in combination with NP-Gem in all randomized patients.	• The incidence and severity of adverse events and serious adverse events, and any clinically meaningful trends in safety parameters.
Exploratory	• To describe the pharmacokinetic profile of quemliclustat.	• Plasma concentration of quemliclustat (via sparse sampling).
	• To compare second progression-free survival (PFS-2) in all randomized patients.	• Second progression-free survival is defined as the time from randomization to the date of the second objective disease progression or death from any cause, whichever comes first.
	• To evaluate the relationship between the tumor tissue and blood-based biomarkers and clinical responses following combination treatment.	• Correlation of clinical response with tumor, tumor microenvironment, and blood biomarkers at baseline and after treatment.

	• To evaluate disease-related symptoms and quality of life based on patient-reported outcomes of quemliclustat + NP-Gem versus placebo + NP-Gem in all randomized patients.	• Time to first deterioration in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer Module (EORTC QLQ-PAN26) sub-scale scores. • Time to first deterioration in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) total and domain scores. • Mean change from baseline of EORTC QLQ-PAN26 sub-scale scores. • Mean change from baseline of EORTC QLQ-C30 total and domain scores. • Mean change from baseline of 5-Level EuroQol-5 Dimension (EQ-5D-5L). • Mean change from baseline of EQ-5D-5L Visual Analogue Scale. • Proportion of patients with meaningful change in each domain of EORTC QLQ-PAN26 and EORTC QLQ-C30 while on treatment.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine 5´-monophosphate
AST	aspartate aminotransferase
C1D1	Cycle 1, Day 1
CI	confidence interval
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D 5L	5-Level EuroQol-5 Dimensions
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FOLFIRINOX	5-fluorouracil, leucovorin, irinotecan, and oxaliplatin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gem	gemcitabine
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy

Abbreviation	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
LTFU	Long-Term Follow-Up
MAD	multiple-ascending dose
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NP	nab-paclitaxel
NP-Gem	nab-paclitaxel and gemcitabine
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
PFS-2	second progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PS	Performance Status
PT	preferred term

Abbreviation	Definition
Q2W	every 2 weeks
Q6W	every 6 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30 Version 3
QLQ-PAN26	Quality of Life Questionnaire-Pancreatic Cancer Module
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCA	synthetic control arm
SFU	Safety Follow-Up
SOA	Schedule of Assessments
SOC	standard-of-care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

3. INTRODUCTION

3.1. Study Rationale

This study is designed as a randomized, placebo-controlled, double-blind, 2-arm, global, multicenter, Phase 3 study in adult patients with treatment-naive metastatic pancreatic ductal adenocarcinoma (mPDAC).

Pancreatic ductal adenocarcinoma (PDAC) accounts for approximately 85% of pancreatic cancers (Rawla, 2019). Pancreatic ductal adenocarcinoma ranks as the third leading cause among cancer associated deaths. Approximately 50% of patients with PDAC are diagnosed in the metastatic setting, which is associated with a 5-year survival rate of only 3% (SEER, 2023). Programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) blocking antibodies have shown remarkable success in other tumor types, but have shown limited efficacy in advanced PDAC, regardless of line of treatment and/or if given in combination with standard-of-care (SOC) chemotherapy (Timmer, 2021; Wainberg, 2020). Therefore, alternative approaches beyond the standard T-cell-based PD-1/PD-L1 checkpoint are required to unlock the potential immune mediated antitumor response in PDAC.

One potential mechanism contributing to the immunosuppressive tumor microenvironment associated with mPDAC is the generation of adenosine, which has been shown to suppress the antitumor immune response (Vigano, 2019). The generation of adenosine is in part mediated by the CD73 ecto-nucleotidase, which converts adenosine 5´-monophosphate (AMP) into adenosine. Nonclinical and clinical studies show that CD73 is upregulated in multiple tumors including PDAC and is associated with shorter survival (Zhao, 2021) and is also abundantly expressed on multiple cell types in PDAC (Faraoni, 2023). To this end, Arcus is developing the novel immunotherapy, quemliclustat, in patients with mPDAC. Quemliclustat is a potent, selective, and reversible inhibitor of CD73 that blocks the conversion of AMP to adenosine, thereby enhancing antitumor adaptive immunity (refer to quemliclustat Investigator's Brochure [IB]). Unlike other immune-enhancing drugs, quemliclustat has not displayed any direct activation of the immune system, either in cell culture or in animals. Rather, similar to PD-1/PD-L1 blocking antibodies, the effects of quemliclustat appear to be very selective through reversal of the immune-suppressive microenvironment found in many solid tumors.

3.1.1. Quemliclustat Background

As of 17 October 2023, a total of 261 patients with metastatic castrate-resistant prostate cancer, gastrointestinal (GI) malignancies, metastatic colorectal cancer, advanced upper GI tract malignancies, or non-small cell lung cancer and 66 healthy participants have been treated with quemliclustat across 7 Arcus-sponsored studies. Quemliclustat has been evaluated as a monotherapy in 2 healthy-volunteer studies. Study AB680CSP0001 was a double-blind, randomized, placebo-controlled, single-ascending dose (SAD) and multiple-ascending dose (MAD) study that investigated the safety, tolerability, and pharmacokinetic (PK) profile of intravenous (IV) quemliclustat. A total of 56 healthy participants were enrolled in the SAD part of the study in which 42 participants were treated with a select dose of quemliclustat ranging from 0.1 to 25 mg and 14 participants were treated with a placebo. A total of 8 participants enrolled in the MAD part of the study, with 6 participants in the 8-mg quemliclustat dose group and 2 participants in the placebo group. The type, frequency, and intensity of treatment-emergent

adverse events (TEAEs) were generally comparable across the quemliclustat and placebo groups. All TEAEs were mild or moderate in severity and most resolved (98% in SAD and 86% in MAD). Study ARC-11 was a double-blind, randomized, placebo-controlled, SAD study investigating the safety and PK profile of 100 or 300 mg oral quemliclustat. Twenty-four participants were enrolled, 18 received quemliclustat, and 6 received placebo (8 participants were randomized to each of the 3 cohorts where 2 participants received placebo and 6 received quemliclustat). Headache (20.8%) and sinus tachycardia (8.3%) were the most frequently reported TEAEs. There were no notable observations in clinical laboratory evaluations, vital signs measurements, or electrocardiograms (ECGs). Overall, both Study AB680CSP0001 and Study ARC-11 demonstrated that quemliclustat is well tolerated across dose levels with no clinically meaningful increase in toxicity with increasing dose levels or multiple dosing. Refer to the IB for additional information regarding Study AB680CSP0001 and Study ARC-11.

A Phase 1 dose-escalation and expansion study (Study ARC-8) of quemliclustat in combination with nab-paclitaxel (NP) and gemcitabine (Gem) (nab-paclitaxel and gemcitabine [NP-Gem]) with or without the anti-PD-1, zimberelimab, was evaluated in patients with mPDAC who had not been previously treated in the metastatic setting. In dose escalation (n = 22), increasing dose levels of quemliclustat from 25 to 125 mg given via IV every 2 weeks (Q2W) was evaluated in combination with zimberelimab and NP-Gem. No dose-limiting toxicities, maximum tolerated dose (MTD), or clinically significant safety findings for quemliclustat were reported in escalation. Overall, the safety profile was consistent with the historical safety data of NP-Gem in mPDAC. Based upon PK and pharmacodynamics (PD), 100-mg quemliclustat was selected as the optimal dose for evaluation in dose expansion (refer to the dosing rationale section in Study ARC-8 for additional details). In dose expansion (including 6 patients from dose escalation), 29 patients received quemliclustat 100 mg IV Q2W plus NP-Gem (triplet treatment) and 87 patients received quemliclustat 100 mg IV Q2W plus NP-Gem plus zimberelimab (quadruplet treatment) for a total of 122 patients (pooled 100-mg treatment). The median overall survival (OS) was 19.4 months for the triplet treatment cohort (n = 29), 13.9 months for the quadruplet (n = 93), and 15.7 months for the pooled (n = 122), which represent a substantial improvement in median OS compared with the historical NP-Gem median OS of 8.5 to 9.2 months (Wainberg, 2023; Von Hoff, 2013). To verify these OS improvements, a synthetic control arm (SCA) approach was used to establish a matching NP-Gem control arm for treatment effect analysis of the triplet and pooled quemliclustat cohorts (Wainberg, 2024). The SCA approach has become a well-established method to mimic randomized controls for estimating investigational treatment efficacy (Yin, 2022; Lim, 2018) and to support regulatory submissions to the Food and Drug Administration (FDA) for various oncology indications (Mishra-Kalyani, 2022; FOCR, 2019). The SCA was constructed from patients treated with NP-Gem in historical clinical trials (HCTs) with propensity score matching to achieve balance in baseline characteristics with Study ARC-8 patients. The SCA analysis was conducted by a third party based upon a prespecified statistical analysis plan. Two SCAs, SCA 1 (N = 29) and SCA 2 (N = 122), were constructed with 1:1 matching for baseline characteristics with the Study ARC-8 triplet cohort and Study ARC-8 pooled cohort (triplet or quadruplet) before the outcome data were unblinded and analyzed. Substantial improvements in OS were observed for both the triplet and pooled cohorts as follows:

- Study ARC-8 Triplet Cohort (quemliclustat plus NP-Gem) showed median OS improvement of 7.4 months (19.4 versus 12.0 months) (hazard ratio [HR] = 0.60; p-value = 0.12) in comparison with SCA 1 (NP-Gem alone, N = 29), with a 40% risk-reduction in death.
- Study ARC-8 Pooled Cohort (quemliclustat plus NP-Gem with or without zimberelimab) showed median OS improvement of 5.9 months (15.7 versus 9.8 months) (HR = 0.63; p-value = 0.003) in comparison with SCA 2 (NP-Gem alone, N = 122), with a 37% risk-reduction in death.

The difference between the triplet and the quadruplet treatment cohorts is largely explained by the imbalance in liver metastasis at baseline. A subgroup analysis by the presence of baseline liver metastasis demonstrated a median OS of 12.1, 11.1, or 12.1 months for the triplet, quadruplet, or pooled treatments if liver metastases were present at baseline and 22, 21.2, or 21.5 months for the triplet, quadruplet, or pooled treatments if liver metastases was not present at baseline. The cumulative analysis of efficacy confirmed that zimberelimab does not demonstrate contribution of components and is therefore not an active component of the combination therapy, consistent with the literature reported findings for other anti-PD-L1 inhibitor treatments evaluated in patients with microsatellite stable/mismatch repair proficient mPDAC (Timmer, 2021; Wainberg, 2020; Pu, 2019). Importantly, the rate of all cause and treatment-related Grade ≥ 3 TEAEs, serious adverse events (SAEs), and TEAEs leading to death or TEAEs leading to treatment discontinuation reported for the quemliclustat combinations from Study ARC-8 was comparable to the historical safety data reported for NP-Gem (Wainberg, 2023; Abraxane, 2022; Von Hoff, 2013) Refer to the IB for additional information regarding the efficacy and safety of quemliclustat in combination with NP-Gem in patients with first-line mPDAC.

Given the substantial improvement in OS with nominal added toxicity, the combination of quemliclustat and NP-Gem offers a favorable risk-benefit profile that warrants further clinical investigation given the limited effective therapeutic options available for patients with mPDAC.

3.2. Pancreatic Ductal Adenocarcinoma Treatment Landscape

In 2020, there were 495,773 new cases of pancreatic cancer, 85% of which are PDAC, and 466,003 associated deaths reported worldwide, making it one of the deadliest forms of cancer (Ilic, 2022; Rawla, 2019). Globally, Europe has the highest age-standardized rate of incidence and mortality and accounts for approximately 29% of global pancreatic cancer-related deaths (Partyka, 2023). In the United States (US), it is estimated that 64,050 new cases of pancreatic cancer were diagnosed in 2023, with 50,550 pancreatic cancer-related deaths (Siegel, 2023). Approximately 50% of patients diagnosed with PDAC are diagnosed in the metastatic setting with a 5-year OS rate of only approximately 3% (SEER, 2023). Given the limited effectiveness and tolerability of available SOC therapies, there remains a high unmet medical need for novel, effective, and tolerable treatment options for patients with mPDAC.

Limited effective treatment options exist for patients with mPDAC, and the past few decades have brought few treatment advances for these patients.

Table 2 summarizes the available systemic therapies or regimens that have been approved or are currently under review by the FDA or European Medicines Agency or recommended by the National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines for the first-line treatment of patients with mPDAC. The median OS reported for Gem, Gem + erlotinib, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), NP-Gem, or liposomal irinotecan (ONIVYDE), fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) was 6.7, 6.5, 11.1, 8.5-9.2, or 11.1 months, respectively (Wainberg, 2023; Abraxane, 2022; Tarceva, 2016; Conroy, 2011). Additional therapies not listed in Table 2 have also been approved and/or recommended by NCCN or ESMO for biomarker select patients but such patients are not relevant to the current Phase 3 study and thus not discussed.

Table 2: Currently Utilized Systemic Therapies and Regimens for First-Line mPDAC

Systemic Therapy	**Approved by FDA and/or EMA; Recommended by NCCN and/or ESMO Guidelines***	**Reported Median OS**
Gemcitabine [a]	Approved by FDA and EMA; NCCN and ESMO recommended	6.7 months
Gemcitabine + erlotinib [b]	Approved by FDA; NCCN recommended	6.5 months
Fluoropyrimidine	Approved by FDA and EMA; NCCN recommended (Category 2B)	Not available
Nab-paclitaxel + gemcitabine [c,d]	Approved by FDA and EMA; NCCN and ESMO recommended (Category 1)	8.5-9.2 months
Capecitabine	EMA Approved; NCCN recommended (Category 2B)	Not available
FOLFIRINOX [c]	ESMO and NCCN recommended (Category 1)	11.1 months
NALIRIFOX [d]	FDA and EMA approved; NCCN Recommended (Category 1)	11.1 months

EMA = European Medicines Agency; ESMO = European Society for Medical Oncology; FDA = Food and Drug Administration; FOLFIRINOX = 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; mPDAC = metastatic pancreatic ductal adenocarcinoma; NALIRIFOX = liposomal irinotecan (ONIVYDE), fluorouracil, leucovorin, and oxaliplatin; NCCN = National Comprehensive Cancer Network; OS = overall survival

*Unless otherwise noted, NCCN Recommended refers to only therapies that are classified as Preferred Regimen or considered to have Category 1 level of evidence per the NCCN.

[a] Abraxane, 2022

[b] Tarceva, 2016

[c] Conroy, 2011

[d] Wainberg, 2023

As shown in Table 2, several systemic therapies are available for mPDAC, all of which are associated with limited long-term survival benefit. Of these, the triplet based cytotoxic regimen, FOLFIRINOX, and doublet based cytotoxic regimen, NP-Gem, have emerged in the past decade as the standard first-line regimens for mPDAC and are recommended by the NCCN as the only two preferred regimens for patients who can tolerate doublet- or triplet-based cytotoxic therapy. Although FOLFIRINOX and NP-Gem have not been directly compared in a clinical study, FOLFIRINOX or NP-Gem demonstrated a median OS of 11.1 or 8.5-9.2 months and median

progression-free survival (PFS) of 6.4 or 5.5 to 5.6 months (Wainberg, 2023; Von Hoff, 2013; Conroy, 2011). FOLFIRINOX and NP-Gem are both associated with relatively high rates of Grade ≥ 3 hematological toxicities. However, FOLFIRINOX is also associated with higher rates of Grade ≥ 3 nonhematological toxicities, including diarrhea and vomiting (Wainberg, 2023; Abraxane, 2022; Tarceva, 2016; Conroy, 2011). Given the higher overall toxicity rates, the use of FOLFIRINOX is limited to patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1, whereas NP-Gem can be tolerably administered to patients with ECOG PS of 0 to 2 (Von Hoff, 2013). Accordingly, the toxicity profile of NP-Gem makes it the preferred SOC option to combine with novel therapies in a safe and effective manner.

3.3. Overall Risk and Benefit Assessment

This study is designed as a randomized, placebo-controlled, double-blind, 2-arm, global, multicenter, Phase 3 study in adult patients with treatment naive mPDAC.

Patients eligible for this study have been diagnosed with mPDAC and have not been previously treated in the metastatic setting. The current SOC for such patients consists of chemotherapy that is associated with limited OS of 9 to 11 months as described in Section 3.2. As described in Section 3.1, quemliclustat in combination with NP-Gem, with or without anti-PD-1, demonstrated a median OS of 15.7 months without a clinically meaningful increase in toxicity.

Given the high unmet medical need for this population and the encouraging safety and efficacy data of quemliclustat in combination with the SOC, NP-Gem, from Study ARC-8, the proposed Phase 3 study will generate clinical data to support a potential safe and effective treatment option for patients with treatment-naive mPDAC. Furthermore, all patients will receive the preferred SOC regimen, NP-Gem, and an independent data monitoring committee (IDMC) will be established to regularly monitor the safety of patients in this study. An interim analysis for OS superiority test is also planned (Section 11.2).

Therefore, the current study is appropriately designed to safeguard patient interest in the evaluation of a potentially new effective treatment for patients with limited effective treatment options.

4. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Primary Objective	**Corresponding Endpoint**
• To compare OS of quemliclustat + NP-Gem vs placebo + NP-Gem in all randomized patients.	• Overall survival is defined as the time from date of randomization until the date of death from any cause.
Secondary Objectives	**Corresponding Endpoints**
• To compare PFS of quemliclustat + NP-Gem vs placebo + NP-Gem in all randomized patients.	• Progression-free survival is defined as the time from the date of randomization until disease progression or death from any cause, whichever comes first, as measured per RECIST v1.1 as assessed by the investigator.
• To assess additional measures of clinical activity in all randomized patients.	• Objective response rate is defined as the proportion of patients who have achieved best overall response of confirmed CR or PR to study therapy as assessed by the investigator according to RECIST v1.1. • Duration of response is defined as the time from the first objective response (CR or PR) until the date of first documented disease progression or death, whichever comes first, as measured per RECIST v1.1 as assessed by the investigator. • Disease control rate is defined as the proportion of patients who have achieved confirmed CR, confirmed PR, or stable disease for ≥ 8 weeks from date of randomization as assessed by the investigator according to RECIST v1.1.
• To assess the safety and tolerability of quemliclustat or placebo in combination with NP-Gem in all randomized patients.	• The incidence and severity of AEs and SAEs and any clinically meaningful trends in safety parameters.

Table 3: Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
• To describe the PK profile of quemliclustat.	• Plasma concentration of quemliclustat (via sparse sampling).
• To compare PFS-2 in all randomized patients.	• Second progression-free survival is defined as the time from randomization to the date of the second objective disease progression or death from any cause, whichever comes first.
• To evaluate the relationship between the tumor tissue and blood-based biomarkers and clinical responses following combination treatment.	• Correlation of clinical response with tumor, tumor microenvironment, and blood biomarkers at baseline and after treatment.
• To evaluate disease-related symptoms and QoL based on PROs of quemliclustat + NP-Gem vs placebo + NP-Gem in all randomized patients.	• Time to first deterioration in EORTC QLQ-PAN26 sub-scale scores. • Time to first deterioration in EORTC QLQ-C30 total and domain scores. • Mean change from baseline of EORTC QLQ-PAN26 sub-scale scores. • Mean change from baseline of EORTC QLQ-C30 total and domain scores. • Mean change from baseline of EQ-5D-5L. • Mean change from baseline of EQ-5D-5L VAS. • Proportion of patients with meaningful change in each domain of EORTC QLQ-PAN26 and EORTC QLQ-C30 while on treatment.

AE = adverse events; CR = complete response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3; EORTC QLQ-PAN26 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer Module; EQ-5D-5L = 5-Level EuroQol-5 Dimension; NP-Gem = nab-paclitaxel and gemcitabine; OS = overall survival; PFS = progression-free survival; PFS-2 = second progression-free survival; PK = pharmacokinetic; PR = partial response; PROs = patient-reported outcomes; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1; SAE = serious adverse events; VAS = visual analogue scale; vs = versus

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a randomized, placebo-controlled, double-blind, 2-arm, global, multicenter, Phase 3 study to evaluate the OS of quemliclustat versus placebo when each is given in combination with SOC NP-Gem in patients with confirmed mPDAC previously untreated in the metastatic setting.

Approximately 610 patients will be enrolled in the study and randomized 2:1 to Arm A or Arm B. Patient randomization will be stratified by presence or absence of liver metastases; ECOG PS score (0 versus 1); and region (North America and Western Europe versus East Asia versus Rest of World). A patient is considered enrolled after completing the informed consent process, meeting all eligibility criteria, none of the exclusion criteria, and being randomized. Refer to Figure 1 for the study design schema.

Arm A (Experimental Arm):

Doses and administration of quemliclustat, NP, and Gem will be administered using a 28-day cycle:

- Quemliclustat administered at 100 mg IV over 30 minutes (± 5 minutes) on Days 1 and 15 of each cycle
- Nab-paclitaxel administered at 125 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle
- Gemcitabine administered at 1000 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle

Arm B (Comparator Arm):

Doses and administration of placebo, NP, and Gem will be administered using a 28-day cycle:

- Placebo administered Q2W IV over 30 minutes (± 5 minutes) on Days 1 and 15 of each cycle
- Nab-paclitaxel administered at 125 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle
- Gemcitabine administered at 1000 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1, 8, and 15 of each cycle

Crossover between the experimental and comparator arms is not allowed.

Patients should continue treatment until permanent treatment discontinuation criteria are met per Section 7.6.1. In addition, the maximum treatment duration for quemliclustat/placebo is 2 years from the initial dose.

An IDMC will be used in this study to monitor the ongoing safety of the investigational product in patients as well as at prespecified interim efficacy analysis as described in the IDMC Charter.

Patients will complete 4 study periods: Screening (up to 28 days prior to Cycle 1, Day 1 [C1D1]), Treatment, Safety Follow-Up (SFU), and Long-Term Follow-Up (LTFU). The Schedule of Assessments (SOA) (Table 4 and Table 5) is shown in Section 5.2. Patients will

follow either Table 4 or Table 5 of the SOA depending upon discontinuation of a study treatment as described in Section 5.2.

Safety measures will be assessed at regular intervals throughout the duration of treatment and during the 30-day SFU period as shown in Table 4 and Table 5. Disease assessments will be performed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) every 8 weeks through Cycle 12 then every 12 weeks thereafter, regardless of treatment delays. Refer to Section 9.4.1 for rules regarding treatment beyond initial radiographic disease progression. Patients who discontinue all study treatments for reasons other than radiographic disease progression (eg, toxicity) will continue to undergo tumor assessments in SFU/LTFU following the interval described in Table 4 or Table 5 until radiographic disease progression, withdrawal of consent, initiation of a new anticancer therapy, lost to follow-up, death, or until the study completes, whichever occurs first. Pharmacokinetic parameters, exploratory biomarkers, and patient-reported outcomes (PROs) will also be assessed at intervals described in Table 4 or Table 5.

In SFU and LTFU, patient survival, changes in subsequent anticancer treatment, and subsequent radiographic disease progression will be assessed every 6 weeks (Q6W) as described in Table 4 and Table 5.

The study design schema is provided in Figure 1.

5.1.1. Scientific Rationale for Study Design

This study is designed as a randomized, placebo controlled, double blind, 2-arm, global, multicenter, Phase 3 study in adult patients with treatment-naive mPDAC.

Randomization is used to minimize bias towards enrollment in each treatment arm and a randomization ratio of 2:1 in favor of the Experimental Arm (Arm A) will provide the opportunity for more patients to receive the SOC in combination with quemliclustat. Double blinding will also be utilized to minimize bias as well as premature patient discontinuation if randomized to the Comparator Arm (Arm B).

Patients will be stratified by presence or absence of liver metastases; ECOG PS score (0 versus 1); and region (North America and Western Europe versus East Asia versus Rest of World). Metastatic liver disease is a recognized key negative prognostic factor for patients with mPDAC and is a standard stratification criteria used in Phase 3 studies (Conroy, 2023). This factor is clearly illustrated in the Study ARC-8 subgroup analysis of median OS by baseline liver metastases in patients with mPDAC, which demonstrates a nearly 10-month difference in median OS based upon the presence/absence of liver metastases (Section 3.1). Patient ECOG PS is a well-validated prognostic factor for most cancer types, including mPDAC (Conroy, 2023). Therefore, stratification by ECOG PS (0 versus 1) is a standard stratification factor used in mPDAC trials to ensure relatively equal distribution of patients based on their overall health. Stratification by region will include North America (US and Canada) and Western Europe versus East Asia versus the Rest of World. Stratification by these regions will help ensure a relatively equal geographic distribution between the two arms based upon consideration for geographical influences on clinical outcomes.

The Experimental Arm (Arm A) is a combination treatment consisting of quemliclustat with the SOC NP-Gem for mPDAC. The choice of the experimental arm is based on promising OS data

observed for quemliclustat + NP-Gem as described in Section 3.1. Nab-paclitaxel in combination with Gem is broadly approved globally and recommended by various regional compendiums, such as NCCN and ESMO, as a SOC for patients with first-line mPDAC. Accordingly, NP-Gem has been chosen as the SOC option to combine with quemliclustat in the experimental arm and will therefore serve as the comparator when given in combination with placebo.

5.1.2. Dose Justification

Doses of quemliclustat in the range of 25 to 200 mg Q2W in combination with NP-Gem with or without zimberelimab have been tested in Study ARC-8. All doses were found to be safe and well-tolerated. No MTD was identified.

Peripheral PD were determined by assessing CD73 enzymatic activity in longitudinal blood samples from healthy volunteers in Study AB680CSP0001 and from patients with mPDAC dosed with quemliclustat in Study ARC-8. The concentration of drug required for ≥ 90% inhibition of CD73 enzyme activity was estimated to be 480 ng/mL. Population PK-based simulations indicated that at steady state, the recommended dose of 100 mg Q2W was the lowest dose that would yield quemliclustat concentrations above the level required to achieve ≥ 90% inhibition of CD73 enzyme activity in majority of patients. Furthermore, exposure-efficacy and exposure-safety analysis of data from Study ARC-8 indicated no statistically significant relationships between measures of exposure metrics (area under the plasma concentration-time curve Cycle 1, minimum observed plasma concentration, maximum observed plasma concentration, and average observed plasma concentration at the time of event) and efficacy and safety (OS, objective response rate [ORR], PFS, Grade ≥ 3 TEAEs), indicating that the 100-mg dose is likely an optimal dose in this patient population.

5.1.3. End of Study Definition

The end of the study is defined as the date on which the last patient in the clinical trial has an assessment (including phone call, public record review, in clinic assessment, etc.) or received study treatment to collect final data for the primary outcome measure, secondary outcome measures, and adverse events, up to 4 years after the last patient first dose of study treatment or the sponsor closes the study.

5.2. Study Design and Schedule of Assessments

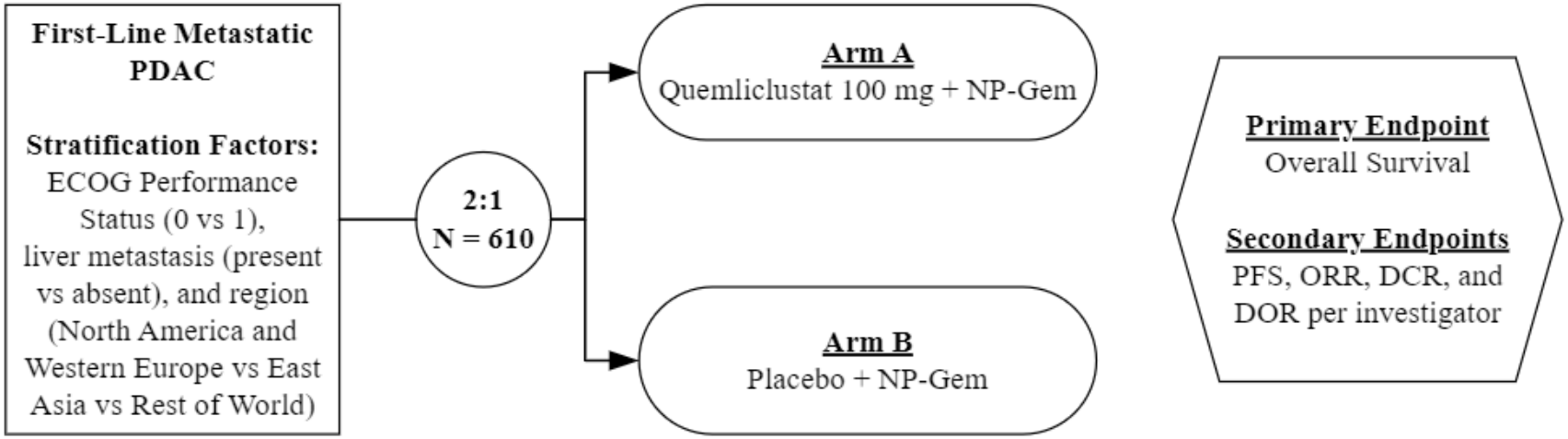
The study design schema is presented in Figure 1.

The SOA are presented in Table 4 and Table 5.

- All patients will follow Table 4 from Screening through Cycle 12 of treatment.
    - Patients who discontinue quemliclustat/placebo prior to completion of Cycle 12 but remain on treatment with NP and/or Gem will continue to follow Table 4 through LTFU.
    - Patients who discontinue all study treatments (quemliclustat/placebo and NP-Gem) prior to completion of Cycle 12 will continue to follow Table 4 through LTFU.

- Patients who remain on treatment with quemliclustat/placebo after Cycle 12 AND who have permanently discontinued NP-Gem will follow the SOA shown in Table 5 for the remainder of treatment with quemliclustat/placebo through LTFU.

Figure 1: Study Design



DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; N = sample size; NP-Gem = nab-paclitaxel and gemcitabine; ORR = objective response rate; PDAC = pancreatic ductal adenocarcinoma; PFS = progression-free survival; vs = versus

Table 4: Schedule of Assessments 1 – Screening Through Cycle 12 (All Patients); Cycle 12 and Beyond (Patients Who Are Still Receiving Quemliclustat/Placebo With NP and/or Gem)

Treatment Cycle (28-day cycle)	**Screening**		**Cycle 1**			**Cycle ≥ 2**			**EOT[a]**	**SFU[a]**	**LTFU**
Cycle Day (visit window in calendar days)	**(-28 to -1 days)**	**(-7 to -1 days)**	**Day 1**	**Day 8 (± 1)**	**Day 15 (± 1)**	**Day 1 (± 2)**	**Day 8 (± 2)**	**Day 15 (± 2)**	**(+ 14)**	**30 days (± 14)**	**Q6W (± 14)**
Assessments/Procedures											
Informed consent	X										
Medical history and demographics	X										
Disease history and prior anticancer therapies	X										
Confirmation of eligibility		X									
Physical exam/symptom-directed (incl. BSA on Day 1 of each cycle)[b]	X		X	X	X	X	X	X	X	X	
Vital signs[c]	X		X	X	X	X	X	X	X	X	
ECOG status		X	X			X			X	X	
12-lead ECG[d]	X										
Concomitant medications	X		X	X	X	X	X	X	X	X	
Adverse events[e]	X		X	X	X	X	X	X	X	X	
Randomization[f]		X									
Safety Laboratory Assessments (local testing)[g]											
Blood collection for hematology		X	X	X	X	X	X	X	X	X	
Blood collection for chemistry		X	X	X	X	X	X	X	X	X	
Blood collection for coagulation		X	X			X			X	X	
Serology[h]	X										
Serum or urine pregnancy test[i]	X		X			X			X	X	
Biomarker/Exploratory Analysis											
Blood collection for PK[j]			Refer to Table 14 for Timepoints								
Blood collection for biomarkers[k]			Predose Day 1 of C1, C2, C3, C7						X		
Archival tumor tissue[k]	X										

Table 4: Schedule of Assessments 1 – Screening Through Cycle 12 (All Patients); Cycle 12 and Beyond (Patients Who Are Still Receiving Quemliclustat/Placebo With NP and/or Gem)

Treatment Cycle (28-day cycle)	**Screening**		**Cycle 1**			**Cycle ≥ 2**			**EOT[a]**	**SFU[a]**	**LTFU**
Cycle Day (visit window in calendar days)	**(-28 to -1 days)**	**(-7 to -1 days)**	**Day 1**	**Day 8 (± 1)**	**Day 15 (± 1)**	**Day 1 (± 2)**	**Day 8 (± 2)**	**Day 15 (± 2)**	**(+ 14)**	**30 days (± 14)**	**Q6W (± 14)**
Study Treatment Administration											
Quemliclustat or placebo[l]			X		X	X		X			
Nab-paclitaxel[l]			X	X	X	X	X	X			
Gemcitabine[l]			X	X	X	X	X	X			
Disease Response/Efficacy Assessments											
CA 19-9 (local laboratory testing)	X		Perform Q8W (± 7 days) from the first dose of study treatment through Cycle 12 and then Q12W (± 7 days) thereafter until radiographic disease progression (patients treated beyond initial progression will continue until a second radiographic disease progression event or study treatment discontinuation, whichever occurs first) withdrawal of consent, initiation of a new anticancer therapy, lost to follow-up, death, or until the study completes, whichever occurs first. Note: CA 19-9 assessment is independent of study cycle.								
Tumor imaging of chest/abdomen/pelvis[m]	X		Perform Q8W (± 7 days) from the first dose of study treatment through Cycle 12 and then Q12W (± 7 days) thereafter until radiographic disease progression (patients treated beyond initial progression will continue until a second disease progression event or until study treatments are discontinued, whichever occur first), withdrawal of consent, initiation of a new anticancer therapy, lost to follow-up, death, or until the study completes, whichever occurs first. Note: Imaging is independent of study cycle or treatment delay.								
Brain imaging[n]	X		As clinically indicated								
Survival follow-up[o]										X	X
Subsequent anticancer treatment[p]										X	X
Subsequent PFS-2 radiographic disease progression[q]										X	X

Table 4: Schedule of Assessments 1 – Screening Through Cycle 12 (All Patients); Cycle 12 and Beyond (Patients Who Are Still Receiving Quemliclustat/Placebo With NP and/or Gem)

Treatment Cycle (28-day cycle)	**Screening**		**Cycle 1**			**Cycle ≥ 2**			**EOT[a]**	**SFU[a]**	**LTFU**
Cycle Day (visit window in calendar days)	**(-28 to -1 days)**	**(-7 to -1 days)**	**Day 1**	**Day 8 (± 1)**	**Day 15 (± 1)**	**Day 1 (± 2)**	**Day 8 (± 2)**	**Day 15 (± 2)**	**(+ 14)**	**30 days (± 14)**	**Q6W (± 14)**
Patient-Reported Outcomes[r]											
EORTC QLQ-PAN26			X			X			X		
EORTC QLQ-C30			X			X			X		
EQ-5D-5L			X			X			X		

AE = adverse event; BSA = body surface area; C1D1 = Cycle 1 Day 1; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PAN26 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer Module; EOT = end of treatment; EQ-5D-5L = 5 Level EuroQol 5 Dimension; Gem = gemcitabine; HIV = human immunodeficiency virus; incl. = includes; LTFU = Long-Term Follow-Up; MRI = magnetic resonance imaging; NP = nab-paclitaxel; PE = physical exam; PFS-2 = second progression-free survival; PK = pharmacokinetic; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SFU = Safety Follow-Up; SOA = Schedule of Assessments

Note: Table 4 will be the SOA followed for screening and Cycles 1-12. After Cycle 12, patients who remain on treatment with NP and/or Gem, will continue to follow the SOA shown in Table 4 until both NP and Gem are discontinued. If after Cycle 12, patients only remain on treatment with quemliclustat/placebo, the SOA shown in Table 5 will be followed.

[a] The EOT visit will be conducted within 14 days of the last dose of all study treatments and prior to the start of new anticancer therapy. The SFU visit must be conducted 30 (± 14) days after the last dose of all study treatments. In instances where the decision to permanently discontinue study treatment is made after 14 days following the last dose of study treatment, the EOT visit is then to be conducted within 14 days of the decision to permanently discontinue study treatment. Procedures performed within 14 days of the EOT visit need not be repeated. If the EOT visit falls within the window of an SFU visit, the EOT visit should be performed and the corresponding SFU visit does not need to be repeated.

[b] A complete PE will be performed at Screening and C1D1. However, if the screening PE occurs within 3 days of C1D1, a brief PE based upon any sign/symptoms exhibited by the patient can instead be conducted. Following C1D1, a brief PE based upon sign/symptoms should be performed at all subsequent timepoints unless a full PE is clinically indicated. Height should be measured at Screening only. Physical examination includes weight and BSA calculation on Day 1 of each cycle. Refer to Section 10.1.2 for PE details.

[c] Vital signs to be collected are temperature, pulse rate, blood pressure, respiratory rate, and pulse oximetry (while the patient is in a seated position). On days where quemliclustat/placebo is administered, vital signs should be assessed up to 60 minutes prior to as well as 30 (± 10) minutes following the quemliclustat/placebo infusion. On visit days where multiple assessments are planned at the same nominal timepoint, vital signs should be performed first, followed by ECG(s), and then blood draws. Vital signs measurements can be performed at any time during the study if clinically indicated.

[d] Triplicate ECGs will be conducted as described in Section 10.1.3 at Screening and as clinically indicated. If an ECG occurs on the same day as study drug administration, then the ECG will be performed first.

[e] Refer to Table 17 for the AE and SAE reporting periods.

[f] Randomization must occur within 3 days prior to C1D1. Randomization can be done the same day as C1D1 but must be completed prior to dosing.
[g] If screening laboratory tests (including pregnancy testing) occur within 3 days of C1D1, they do not need to be repeated on C1D1. Additionally, safety laboratory tests can be performed up to 3 days prior to any dosing visit. The investigator or qualified designee must review results of all required laboratory tests prior to administration of any study treatment. Refer to Appendix 3 for a list of safety laboratories. If a patient does not satisfy any of the eligibility requirements during the initial screening assessment, any relevant assessment(s) may be repeated as needed during the screening window (Day -28 to Day -1) and prior to submission of the patient's eligibility to the sponsor. Otherwise, the patient will be considered a screen failure.
[h] No hepatitis or HIV testing is required unless mandated by local health authority or the patient has history of such infection(s).
[i] For women of childbearing potential only, a serum pregnancy test must be performed at Screening and prior to dosing on C1D1. A serum or urine pregnancy test can be performed at all other study visits where pregnancy testing is indicated.
[j] Refer to Table 14 for PK sampling timepoints and Section 10.2 for sample collection details.
[k] Refer to Section 10.3 and the laboratory manual for details on blood sampling and archival tissue for biomarker analysis. Blood samples should be collected on dosing days before the administration of any study treatment at the indicated timepoints, where applicable.
[l] Quemliclustat/placebo, NP, and/or Gem will be administered as described in Section 7. Refer to Section 7.2 regarding treatment modification and/or delay of quemliclustat/placebo, NP, and/or Gem.
[m] Refer to Section 9.4 for details regarding radiographic imaging methodology. Radiographic imaging performed as standard-of-care prior to obtaining informed consent and within 28 days of the C1D1 do not have to be repeated and can be used as the baseline disease assessment.
[n] Brain imaging (brain MRI or CT scan with contrast if a brain MRI is contraindicated) will be conducted at Screening and during treatment only if symptoms are suggestive of the development of brain metastases. Radiographic imaging performed as standard-of-care prior to obtaining informed consent and within 28 days of the C1D1 do not have to be repeated and can be used as the baseline disease assessment. Refer to Section 9.4 for details regarding radiographic imaging methodology.
[o] Survival follow-up information will be collected Q6W (via telephone calls, patient medical records, and/or clinic visits) until discontinuation from study as described in Section 7.6.2. The survival status of a patient can be collected at any point during the study and during the SFU period.
[p] Subsequent anticancer treatment information will be collected Q6W as described in Section 9.2 and until the patient is discontinued from the study as described in Section 7.6.2.
[q] Subsequent PFS-2–related radiographic disease progression will be assessed Q6W as described in Section 9.3.
[r] The patient-reported outcome assessments will be conducted before other study procedures occur, including study drug administration. Patient-reported outcome assessments may be conducted after safety laboratory assessments in the case when those assessments are performed in the 3 days prior to a dosing visit.

Table 5: Schedule of Assessments 2 – Patients Only On Treatment With Quemliclustat/Placebo After Cycle 12

Treatment Cycle (28-day cycle)	**Cycles 13 - 24**		**EOT[a]**	**SFU[a]**	**LTFU**
Cycle Day (visit window in calendar days)	**Day 1 (± 1)**	**Day 15 (± 1)**	**(+ 14)**	**30 days (± 14)**	**Q6W (± 14)**
Assessments/Procedures					
Physical exam/symptom-directed (incl. BSA on Day 1 of each Cycle)[b]	X	X	X	X	
Vital signs[c]	X	X	X	X	
ECOG status	X		X	X	
12-lead ECG[d]					
Concomitant medications	X	X	X	X	
Adverse events[e]	X	X	X	X	
Safety Laboratory Assessments (local testing)[f]					
Blood collection for hematology	X	X	X	X	
Blood collection for chemistry	X	X	X	X	
Blood collection for coagulation	X		X	X	
Serum or urine pregnancy test[g]	X		X	X	
Biomarker/Exploratory Analysis					
Blood collection for PK[h]		Refer to Table 14 for Timepoints			
Blood collection for biomarkers[i]			X[j]		
Study Treatment Administration					
Quemliclustat or placebo[k]	X	X			
Disease Response/Efficacy Assessments					
CA 19-9 (local laboratory testing)	Perform Q12W (± 7 days) until radiographic disease progression (patients treated beyond initial progression will continue until a second disease progression event or until study treatments are discontinued, whichever occurs first), withdrawal of consent, initiation of a new anticancer therapy, lost to follow-up, death, or until the study completes, whichever occurs first. Note: CA 19-9 assessment is independent of study cycle.				
Tumor imaging of chest /abdomen/pelvis[l]	Perform Q12W (± 7 days) until radiographic disease progression (patients treated beyond initial progression will continue until a second disease progression event or until study treatments are discontinued, whichever occurs first), withdrawal of consent, initiation of a new anticancer therapy, lost to follow-up, death, or until the study completes, whichever occurs first. Note: Imaging is independent of study cycle or treatment delay.				

Table 5: Schedule of Assessments 2 – Patients Only On Treatment With Quemliclustat/Placebo After Cycle 12

Treatment Cycle (28-day cycle)	**Cycles 13 - 24**		**EOT[a]**	**SFU[a]**	**LTFU**
Cycle Day (visit window in calendar days)	**Day 1 (± 1)**	**Day 15 (± 1)**	**(+ 14)**	**30 days (± 14)**	**Q6W (± 14)**
Brain imaging[m]	As clinically indicated				
Survival follow-up[n]				X	X
Subsequent anticancer treatment[o]				X	X
Subsequent PFS-2 radiographic disease progression[p]				X	X
Patient-Reported Outcomes[q]					
EORTC QLQ-PAN26	X		X		
EORTC QLQ-C30	X		X		
EQ-5D-5L	X		X		

AE = adverse event; BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PAN26 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer Module; EOT = end of treatment; EQ-5D-5L = 5 Level EuroQol 5 Dimension; incl. = includes; LTFU = Long Term Follow-up; MRI = magnetic resonance imaging; PE = physical examination; PFS-2 = second progression-free survival; PK = pharmacokinetic; Q6W = every 6 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SFU = Safety Follow-Up; SOA = Schedule of Assessments

Note: Patients who remain on treatment with quemliclustat/placebo after Cycle 12 AND who have permanently discontinued NP-Gem will follow the SOA shown in Table 5 for the remainder of treatment with quemliclustat/placebo and through LTFU.

[a] The EOT visit will be conducted within 14 days of the last dose of all study treatments and prior to the start of new anticancer therapy. The SFU visit must be conducted 30 (± 14) days after the last dose of all study treatments. In instances where the decision to permanently discontinue study treatment is made after 14 days following the last dose of study treatment, the EOT visit is then to be conducted within 14 days of the decision to permanently discontinue study treatment. Procedures performed within 14 days of the EOT visit need not be repeated. If the EOT visit falls within the window of an SFU visit, the EOT visit should be performed, and the corresponding SFU visit does not need to be repeated.

[b] A brief PE based upon sign/symptoms should be performed unless a full PE is clinically indicated. Height should be measured at Screening only. Physical examination includes weight and BSA calculation on Day 1 of each cycle.

[c] Vital signs to be collected are temperature, pulse rate, blood pressure, respiratory rate, and pulse oximetry (while the patient is in a seated position). On days where quemliclustat/placebo is administered, vital signs should be assessed up to 60 minutes prior to as well as 30 (± 10) minutes following the quemliclustat/placebo infusion. On visit days where multiple assessments are planned at the same nominal timepoint, vital signs should be performed first, followed by ECG(s), and then blood draws. Vital signs measurements can be performed at any time during the study if clinically indicated.

[d] Triplicate ECGs will be conducted as clinically indicated as described in Section 10.1.3. If an ECG occurs on the same day as study drug administration, then the ECG will be performed first.

[e] Refer to Table 17 for the AE and SAE reporting periods.
[f] Safety laboratory tests can be performed up to 3 days prior to any dosing visit. The investigator or qualified designee must review results of all required laboratory tests prior to administration of any study treatment. Refer to Appendix 3 for a list of safety laboratories.
[g] For women of childbearing potential only, a serum or urine pregnancy test must be performed at Day 1 of each cycle.
[h] Refer to Table 14 for PK sampling timepoints and Section 10.2 for sample collection details.
[i] Refer to Section 10.3 and laboratory manual for details on blood sampling for biomarker analysis. Blood samples should be collected on dosing days before the administration of any study treatment at the indicated timepoints, where applicable.
[j] The biomarker sample must be taken before the patient is started on any subsequent therapy (systemic, radiation, or surgery).
[k] Quemliclustat/placebo will be administered as described in Section 7. Refer to Section 7.2.1 regarding treatment modification and/or delay of quemliclustat/placebo.
[l] Refer to Section 9.4 for details regarding radiographic imaging methodology.
[m] Brain imaging (brain MRI or CT scan with contrast if a brain MRI is contraindicated) will be performed during treatment only if symptoms are suggestive of the development of brain metastases. Refer to Section 9.4 for details regarding radiographic imaging methodology.
[n] Survival follow-up information will be collected Q6W (via telephone calls, patient medical records, and/or clinic visits) until discontinuation from the study as described in Section 7.6.2. The survival status of a patient can be collected at any point during the study and during the SFU period.
[o] Subsequent anticancer treatment information will be collected Q6W as described in Section 9.2 and until the patient is discontinued from the study as described in Section 7.6.2.
[p] Subsequent PFS-2–related radiographic disease progression will be assessed Q6W as described in Section 9.3.
[q] The patient-reported outcome assessments will be conducted before other study procedures occur, including study drug administration. Patient-reported outcome assessments may be conducted after safety laboratory assessments in the case when those assessments are performed in the 3 days prior to a dosing visit.

6. STUDY POPULATION

6.1. Recruitment and Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The investigator must verify that the patient satisfies all eligibility criteria, and document approval to enroll the patient before the patient can be randomized in the interactive response technology (IRT) system. Every effort will be made to enroll a diverse patient population.

6.2. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

1. Age ≥ 18 years (or age greater than or equal to regionally approved age of consent for participation in investigational clinical studies) at the time of signing the informed consent.
2. Capable of giving signed informed consent, either personally or through a legally authorized representative, that includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
3. Have histologically or cytologically confirmed PDAC that is metastatic.
4. If available, archival tumor tissue sample must be provided for future tumor biomarker analysis per Section 10.3.1. If archival tissue sample is not available, a new biopsy is not required.
5. Have not been previously treated for PDAC in the metastatic setting.
    a. Prior neoadjuvant and/or adjuvant therapy for PDAC is permitted if completed at least 12 months before randomization.
    b. Prior palliative radiotherapy is allowed if completed at least 2 weeks prior to randomization and adverse events (AEs) have resolved to Grade 1 or less before randomization. Prior and/or placement of a biliary stent/tube is permitted if any treatment-related AEs have improved to Grade ≤ 1 and the patient is not exhibiting any signs/symptoms of biliary obstruction.
6. Eastern Cooperative Oncology Group PS of 0 to 1 within 7 days of randomization.
7. At least 1 target lesion measurable by computed tomography (CT)/magnetic resonance imaging (MRI) per RECIST v1.1. not within a field of prior radiation therapy.
8. Adequate organ and marrow function, as defined by the following laboratory values ≤ 7 days prior to randomization:
    a. Neutrophils: ≥ 1500/μL (without myeloid growth factor support within the last 14 days).
    b. Platelets: ≥ 100×10^3/μL (without thrombopoietic stimulating agents or transfusion within the last 14 days).
    c. Hemoglobin: ≥ 9.0 g/dL (without erythropoietin or erythropoietin-stimulating agents or transfusion within the last 14 days).

d. Aspartate aminotransferase (AST): ≤ 2.5 × upper limit of normal (ULN) without hepatic metastasis; ≤ 5 × ULN with hepatic metastasis.
e. Alanine aminotransferase (ALT): ≤ 2.5 × ULN without hepatic metastasis, ≤ 5 × ULN with hepatic metastasis.
f. Total bilirubin: ≤ 1.5 × ULN.
g. Creatinine clearance: ≥ 30 mL/min (calculated using the Cockcroft-Gault method).
h. Albumin: ≥ 3 g/dL within 7 days prior to randomization (without albumin transfusion within the last 2 weeks).

9. Acceptable coagulation status as indicated by an international normalized ratio (INR) ≤ 1.5 × ULN obtained ≤ 7 days prior to randomization. Patients on anticoagulation with INR > 1.5 × ULN can be included at the discretion of the investigator.
10. Women of childbearing potential (as defined in Appendix 2) must have a negative serum pregnancy test.
11. Female patients must not be breastfeeding at the time of providing informed consent and throughout the study.
12. Male and female patients must agree to follow contraception guidelines as detailed in Appendix 2.

6.3. Exclusion Criteria

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

1. Unwilling or unable to comply with study procedures and/or study visits, including subsequent treatment data collection for the second progression-free survival (PFS-2) endpoint, SFU, and LTFU for survival.
2. Previously treated for locally advanced, unresectable PDAC.
3. History of brain metastases or leptomeningeal metastases.
4. Prior treatment with a CD73 antagonist or inhibitor.
5. Underlying medical or psychiatric conditions that, in the investigator or sponsor's opinion, will make the administration of study-specified therapy hazardous or have any of the following:
   a. Interstitial lung disease, including history of non-infectious pneumonitis.
   b. Active viral, bacterial, or fungal infections requiring parenteral treatment within 14 days of randomization.

      Note: Prophylactic antibiotic treatment (eg, to prevent a urinary tract infection) is allowed.
   c. Clinically significant cardiovascular disease, such as New York Heart Association Class III or greater cardiac disease or cerebrovascular accident within 90 days prior to randomization, unstable angina, or new onset angina within 90 days prior to randomization, myocardial infarction within 180 days prior to randomization, or unstable arrhythmia within 90 days prior to randomization.
   d. History of prior solid-organ transplantation, including allogenic bone marrow transplantation.

e. Any clinically significant acute GI symptoms of Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 (eg, nausea, vomiting, diarrhea).
f. Known active mental, psychiatric, or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

6. History of ascites requiring therapeutic paracenteses or diuretics.
7. History of trauma or major surgery within 28 days prior to randomization.

   Note: Placement of central venous access catheter (eg, port or similar) or biliary stent is not considered a major surgical procedure.

8. QTc ≥ 470 msec using Fredericia's QT correction formula (based on an average of triplicate recordings) within 28 days prior to randomization.
9. Any active autoimmune disease or a documented history of autoimmune disease or syndrome that required systemic treatment in the past 2 years prior to randomization (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs), except for vitiligo or resolved childhood asthma/atopy.

   a. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment as listed above.

10. Patients with a condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) within 14 days, another nonexperimental immunosuppressive medication within 30 days, or an experimental immunosuppressive medication within 5 half-lives of randomization. Inhaled or topical steroids and adrenal replacement steroid doses (≤ 10 mg daily prednisone equivalent) are permitted in the absence of active autoimmune disease.
11. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix, breast, or prostate cancer. Furthermore, indolent malignancies, including but not limited to early-stage chronic lymphocytic leukemia, follicular lymphoma, and watch-and-wait eligible prostate cancer, that do not require anticancer treatment, may be allowed after discussion with the medical monitor.
12. Known hypersensitivity to any of the components for any of the study interventions.
13. There is presence of any contraindications outlined in the contraindications or warnings and precautions sections of the product prescribing information for NP or Gem.
14. Uncontrolled infection with human immunodeficiency virus (HIV). Patients on stable highly active antiretroviral therapy (HAART) therapy for ≥ 4 weeks prior to randomization with undetectable viral load and CD4 + T-cell count ≥ 350 cells/μL will not be excluded.

    Note: HIV testing at screening is not required unless mandated by local health regulations or patient has a history of HIV.

15. Known acute hepatitis B, known chronic hepatitis B infection with active untreated disease, or known active hepatitis C infection. Patients with a history of treated hepatitis B virus (HBV) or hepatitis C virus (HCV) who have no detectable viral load by polymerase chain reaction (PCR) will not be excluded.

    Note: HBV or HCV testing at screening is not required unless mandated by local health regulations or patient has a history of HBV or HCV infection.

7. STUDY TREATMENTS

7.1. Study Treatments Administered

Table 6: Study Treatments Administered

Treatment Name	Quemliclustat	Nab-Paclitaxel	Gemcitabine	Placebo
Type	Drug	Drug	Drug	Placebo (Normal Saline)
Dosage level	100 mg	125 mg/m^2	1000 mg/m^2	N/A
Arm	Arm A	Arm A and B	Arm A and B	Arm B
Dosing interval	Days 1 and 15 (Q2W) of each cycle	Days 1, 8, and 15 of each cycle	Days 1 ,8, and 15 of each cycle	Days 1 and 15 (Q2W) of each cycle
Cycle length	28 Days	28 Days	28 Days	28 Days
Route of administration	IV	IV	IV	IV
Drug brand	N/A	Nab-paclitaxel (generic or any brand name), approved by the local Health Authority in the country of randomization for use in patients with mPDAC	Gemcitabine (generic or any brand name), approved by the local Health Authority in the country of randomization for use in patients with mPDAC	N/A
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee depending on local country operational or regulatory requirements	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee depending on local country operational or regulatory requirements	Provided locally by the trial site, subsidiary, or designee

IV = intravenous; mPDAC = metastatic pancreatic ductal adenocarcinoma; N/A = not applicable; Q2W = every 2 weeks

Generic or any brand name nab-paclitaxel are interchangeable during the treatment period provided they are approved by the local health authority in the country of randomization for use in patients with mPDAC.

Generic or any brand name gemcitabine are interchangeable during the treatment period provided they are approved by the local health authority in the country of randomization for use in patients with mPDAC.

Administration of a study drug will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Dosing Instructions:

- If quemliclustat/placebo is administered on the same day as NP and Gem, the study treatments must be administered in the following order as described:
  - Administer 100 mg quemliclustat/placebo IV over a 30-minute (± 5 minutes) period followed by a 30-minute (+ 15 minutes) rest interval
  - Administer NP 125 mg/m^2 IV over a 30-minute (± 5 minutes) period or per institutional guidelines
  - Administer Gem 1000 mg/m^2 IV over a 30-minute (± 5 minutes) period or per institutional guidelines immediately after NP
- If only NP and Gem are administered on a given study day, the study treatments must be administered in the following order as described:
  - Administer NP 125 mg/m^2 IV over a 30-minute (± 5 minutes) period or per institutional guidelines
  - Administer Gem 1000 mg/m^2 IV over a 30-minute (± 5 minutes) period or per institutional guidelines immediately after NP

The decision to administer a given study treatment will be dictated by the criteria described in Section 7.6.1 and Section 7.2.

Specific instructions regarding quemliclustat/placebo preparation and administration are described in the Pharmacy Manual or in the relevant prescribing information for NP and Gem according to institutional standard practice.

7.2. Treatment Modification Criteria

An AE related to a given study drug may require treatment modification of the study drug in the form of dose modification, dose delay and/or dose interruption, or permanent discontinuation of the study treatment.

Temporary dose delay is defined as an intentional delay in the scheduled administration of a study treatment (eg, stopping treatment during a cycle or delaying the start of a new cycle until toxicity resolves). Dose delays for reasons other than an AE, such as a surgical procedure, may be allowed with medical monitor approval. If a dose of study drug cannot be administered per the protocol specified timepoint, the dose will be skipped and upon resumption of treatment, the patient would resume dosing at the next regularly scheduled treatment administration timepoint per Table 4 or Table 5. Skipped doses of a study drug will not be made up. During a treatment delay, the SOA will continue to be followed as described in Table 4 and Table 5.

Dose interruption is defined as an interruption of an infusion while it is being administered to a patient intravenously.

The investigator may attribute each AE to a single study drug or multiple study drugs in the combination. The study drug(s) attributed to the AE will be delayed or modified where required according to Section 7.2.1 for quemliclustat and Section 7.2.2 for NP-Gem. Modification, delay, or permanent discontinuation of one study drug does not require a reciprocal action of the remaining study drugs unless otherwise stated in Section 7.2.1 and Section 7.2.2.

For the management/treatment of AEs, including infusion-related reactions, and/or signs/symptoms thereof, local guidelines (eg, ESMO, NCCN, American Society of Clinical Oncology [ASCO], etc.) and/or institutional standard practice will be followed.

7.2.1. Treatment Modification of Quemliclustat

Treatment modification of quemliclustat due to an AE, including for infusion-related reactions, is described in Appendix 1, which is intended to provide guidance on how to manage quemliclustat for a given AE.

Dose delays of quemliclustat due to an AE are allowed for no more than 42 consecutive days. If quemliclustat has been delayed more than 42 days, quemliclustat should be permanently discontinued. However, if the investigator feels that the patient may still potentially benefit from additional treatment after 42 days, resumption of study treatment may occur if approved by the sponsor's medical monitor or designee. During a treatment delay, the SOA will continue be followed as described in Table 4 and Table 5.

The dose of quemliclustat may be reduced up to 2 times as outlined in Table 7. Dose re-escalation is not allowed.

Table 7: Recommended Dose Reductions for Quemliclustat

	Initial Dose Level	First Dose Reduction	Second Dose Reduction
Quemliclustat	100 mg	75 mg	50 mg

7.2.2. Treatment Modification for Nab-Paclitaxel and Gemcitabine

The treatment modification guidelines for NP and Gem described in this section are consistent with those outlined in the NP prescribing information (Abraxane, 2022) and must be adhered to for the duration of a patients treatment with NP and/or Gem on study.

A treatment delay of NP and/or Gem is allowed for up to 28 consecutive days for recovery of an AE. If the patient is unable to resume treatment with NP or Gem, the delayed study treatment will be discontinued.

Dose level reductions for NP or Gem are provided in Table 8 with a maximum reduction of 2 dose levels each for NP or Gem. Neither NP nor Gem can be re-escalated following a dose reduction.

Table 8: Dose Level Reductions for Nab-Paclitaxel or Gemcitabine

Dose Level	Nab-Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
First dose reduction	100	800
Second dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

7.2.2.1. Hematological Toxicity

Treatment modification of NP and Gem due to neutropenia or thrombocytopenia and for febrile neutropenia are provided in Table 9 and Table 10, respectively. Treatment modification of NP and Gem should not occur prior to a patient's neutrophil or platelet count meeting the criteria described in Table 9. However, if, in the opinion of the investigator, the patient's safety is at risk, treatment modification is allowed as needed per the investigator's medical judgement. In such cases, the investigators medical rationale should be documented in the source records and appropriate electronic case report form (eCRF).

Table 9: Treatment Modification of NP and Gem for Neutropenia and/or Thrombocytopenia at the Start of or Within a Cycle

Cycle Day	Absolute Neutrophil Count (cells/mm^3)		Platelet Count (cells/mm^3)	Action Taken With NP and Gem
Day 1	< 1500	OR	< 100000	Delay doses until recovery
Day 8	500 to < 1000	OR	50000 to < 75000	Reduce 1 dose level
	< 500	OR	< 50000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50000 to < 75000	Reduce 1 dose level from Day 8
	< 500	OR	< 50000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50000 to < 75000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50000	Withhold doses

NP = nab-paclitaxel; Gem = gemcitabine

Table 10: Treatment Modification of NP and Gem for Febrile Neutropenia

Adverse Event	Action Taken With NP and Gem
Febrile neutropenia (Grade 3 or 4)	Withhold until fever resolves and absolute neutrophil count ≥ 1500; resume at next lower dose level
Recurrent febrile neutropenia (Grade 3 or 4)	Withhold until fever resolves and absolute neutrophil count ≥ 1500; Resume at two dose levels lower each for NP (ie, 75 mg/m^2) and Gem (ie, 600 mg/m^2)

NP = nab-paclitaxel; Gem = gemcitabine

7.2.2.2. Nonhematological Toxicity

Treatment modification for most nonhematologic AEs that occur despite adequate background medical therapy should be undertaken in accordance with Table 11. Additionally, there are specific treatment modification and discontinuation guidelines for the nonhematological AEs of cutaneous toxicity, gastrointestinal toxicity, pneumonitis, hypersensitivity reaction, and infusion-related reactions. See Table 12 for corresponding treatment modification guidelines unique to these AEs.

Unless otherwise specified below, dose delay, dose reduction, or permanent discontinuation of NP does not require a reciprocal action for Gem and vice versa. The decision to delay, dose reduce, or permanently discontinue NP, Gem, or both NP and Gem should be dictated by the causality to NP or Gem. However, the investigator may delay, reduce, or permanently discontinue both NP and Gem regardless of causality per the investigator's medical judgement.

Table 11: Treatment Modification of NP and/or Gem for Nonhematologic AE

AE Grade or Dose Delay Duration	Action Taken With NP and/or Gem
Grade 0, 1, or 2	No treatment modification required unless otherwise described in Table 12
Grade 3[a]	Delay NP and/or Gem as appropriate until resolution to Grade ≤ 1; resume at one dose level lower for NP and/or Gem with the following considerations: • Peripheral neuropathy, only NP needs to be withheld and resumed at next lower dose level • Excludes alopecia
Grade 4	Permanently discontinue with the following exceptions • Peripheral neuropathy: No change to Gem required; NP must be delayed until resolution to Grade ≤ 1 and can be resumed at one dose level lower • Excludes alopecia

AE = adverse event; NP = nab-paclitaxel; Gem = gemcitabine

[a] The decision to delay/dose reduce/discontinue NP, Gem, or both NP and Gem should be dictated by the causality to NP and/or Gem but the investigator may delay/dose reduce/discontinue both NP and Gem regardless of causality per the investigator's medical judgement.

Table 12: Specific Treatment Modification and Discontinuation Guidelines

Adverse Event	Action Taken With NP and/or Gem
Cutaneous Toxicity	Patients who develop Grade 2 or 3 cutaneous AE will have both the NP and Gem dose reduced to the next lower dose level. If the patient continues to experience these reactions despite dose reduction, NP and Gem should be discontinued. Patients who develop Grade 4 cutaneous toxicity will have study treatment discontinued.
Gastrointestinal Toxicity	If Grade 2 mucositis or diarrhea occurs, delay both NP and Gem until resolution to Grade ≤ 1, then resume at the next lower dose levels. Treatment with both NP and Gem will be discontinued for Grade ≥ 3 mucositis or diarrhea.
Pneumonitis	Monitor patients for signs and symptoms of pneumonitis and interrupt both NP and Gem during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue NP and Gem.
Hypersensitivity Reaction	Hypersensitivity reactions are not usually expected with NP or Gem. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate discontinuation of the offending agent (ie, NP or Gem) and aggressive symptomatic therapy.
Infusion-Related Reactions	For Grade 3 or 4 infusion-related reactions, discontinue treatment of the offending agent (ie, NP or Gem).

AE = adverse event; Gem = gemcitabine; NP = nab-paclitaxel

7.2.3. Overdose

For this study, overdose is defined as the following:

- Quemliclustat: > 200% of the protocol-designated dose
- Nab-paclitaxel: > 110% of the protocol-designated dose
- Gemcitabine: > 110% of the protocol-designated dose

In the event of an overdose, the investigator should:

1. Notify the medical monitor (or their designee) immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities.
3. Institute symptom-directed supportive care in accordance with institutional standard practice.
4. Document the quantity of the excess dose as well as the duration of the overdose. Report the incident on the SAE report form and report to the sponsor as described in Section 10.4.8.

Decisions regarding dose delay or modifications will be made by the investigator in consultation with the medical monitor (or their designee) based on the clinical evaluation of the patient.

Details of signs and symptoms, clinical management, and outcome should be reported, if applicable, and should follow guidelines in Section 10.4.8. Overdoses should also be captured as protocol deviations.

7.3. Concomitant Therapy

Concomitant medications include any drugs taken in addition to the study drug; these include prescription or over-the-counter medications. At each visit, patients will be asked whether they have taken any medication other than the study drug, and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, will be recorded in the eCRF. Documentation should include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.3.1. Permitted Therapy

Concomitant medications or treatments, including hematopoietic growth factors, may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 7.3.2. Concomitant use of therapies that contain cannabinoids is permitted based on the investigator's discretion and state and local regulations.

Palliative radiotherapy (eg, treatment of known bone metastases) is allowed provided it does not interfere with assessment of tumor target lesions and is approved by the sponsor medical monitor or designee. Patients should be closely monitored for any potential toxicity during and after receiving radiotherapy.

The metabolism of paclitaxel is catalyzed by cytochrome P450 (CYP)2C8 and CYP3A4. Though not prohibited, caution should be exercised when administering NP concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

7.3.2. Prohibited Therapy

The medications/treatments listed below are prohibited during the study. If there is a clinical indication requiring treatment with a prohibited therapy to maintain the welfare of the patient, the patient should be treated as needed. However, as described below, the use of certain prohibited therapy(s) will result in treatment discontinuation. The sponsor must be notified if a patient receives any of these during the study.

- Any concurrent anticancer therapy, including, but not limited to, surgery to remove tumor(s), chemotherapy (other than the chemotherapy administered with study treatment), radiotherapy (except palliative radiotherapy), immunotherapy (other than the immunotherapy administered with study treatment), biologic, hormonal treatment (concurrent use of hormones for noncancer-related conditions is permitted). Study treatment(s) will be discontinued (as described in Section 7.6.1) if patients receive a non-protocol specified concurrent anticancer therapy.
- Use of systemic immunosuppressive medications, including systemic corticosteroids at supra-physiologic doses (supra-physiologic doses being equivalent to a dose of > 10 mg oral prednisone or equivalent) with the following exceptions:

  - Treatment of immune-mediated AEs
  - A temporary course to avoid allergic reaction (eg, IV contrast dye or transfusions) may be permitted, depending on the duration and dose, after discussion and agreement with the medical monitor (or their designee).
  - For chemotherapy induced nausea/vomiting, corticosteroids may be given the day of chemotherapy administration. Nonsteroidal anti-emetic therapy (eg, palonosetron, fosaprepitant, olanzapine, etc.) should also be given as a premedication, preferably IV, before administration of chemotherapy and at home (oral version) for 2 days thereafter. Patients who continue to experience nausea/vomiting despite adequate nonsteroidal anti-emetic therapy can receive corticosteroid treatment for up to 2 additional days following each administration of chemotherapy upon approval from the medical monitor.

- Live vaccines through 30 days after the last dose of study intervention.
- In addition to the above prohibited medications, many herbal and natural remedies have effects on the PK of anticancer medicines and should be discouraged. Specific medications can be discussed with the medical monitor (or their designee).
- Any medication prohibited in combination with chemotherapy as described in the respective prescribing information for NP or Gem unless such study treatments have been permanently discontinued.

7.4. Treatment Compliance

Study treatment is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study patient according to the study protocol. Only patients enrolled in the study may receive investigational product and only authorized site staff may dispense or administer investigational product.

All study treatments will be administered at the site under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and patient 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.

7.5. Randomization, Stratification, and Blinding

After informed consent has been obtained and once deemed eligible for entry into the study, patients will be randomized in a 2:1 ratio to quemliclustat plus NP-Gem or placebo plus NP-Gem, respectively, using the IRT system. Treatment randomization will be stratified according to the following factors:

- ECOG PS (0 versus 1)
- Liver metastases (present versus absent)
- Region (North America + Western Europe versus East Asia versus Rest of World)

7.5.1. Blinding and Unblinding

This is a double-blinded study. To maintain the blind, quemliclustat and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist at the study site. The unblinded pharmacist will obtain each patient's study identification number and study-drug assignment from the IRT and prepare study treatment solutions for infusion. The unblinded pharmacist will provide the blinded study-site staff with ready-to-use, blinded, and identically packaged quemliclustat/placebo infusion solutions for administration at scheduled infusion visits. The sponsor and its personnel (with the exception of select designated agents such as the IRT service provider, PK/PD laboratory personnel, IDMC members, etc.), the study site personnel (excluding the unblinded pharmacist), and the patient will be blinded to quemliclustat versus saline placebo administration.

In the event of a medical emergency or pregnancy in which knowledge of the investigational product (ie, quemliclustat versus placebo) will alter the immediate medical management of the patient, emergency unblinding of the patient may be performed by the investigator. Although not required, it is also strongly recommended that the decision to unblind a patient's treatment assignment first be discussed with the medical monitor. Patients whose treatment assignment is unblinded will be discontinued from further treatment with quemliclustat/placebo. However, patients will be allowed to continue with NP-Gem following resolution of the AE to baseline or Grade ≤ 1 if the AE is unrelated to NP-Gem per investigator assessment and the medical monitor has reviewed and agreed with the lack of causality for NP-Gem. If these conditions for continuing NP-Gem are not met before the patients exceeds the maximum 28-day treatment delay allowed for NP-Gem, NP-Gem will be permanently discontinued. Please consult the IRT manual regarding how to unblind the patient's treatment assignment in IRT.

Patients with disease progression and who are considering subsequent treatment in a clinical trial that requires knowledge of prior treatment with an adenosine pathway modulator or related mechanism (eg, immunotherapy), unblinding of the patient's treatment assignment may be allowed following approval from the medical monitor or designee. Upon approval from the medial monitor or designee, the investigator can unblind the patient's treatment assignment through the IRT as described in the IRT manual.

In the event of a patient's unblinding by the investigator, the sponsor will remain blinded.

While the trial is ongoing, requests for unblinding for reasons other than those specified above will not be permitted unless required by regulatory authorities. Any planned or unplanned unblinding, including accidental or emergency unblinding, should be reported, documented, and assessed for impact to trial results.

7.6. Discontinuation of Study Treatment and Study Withdrawal

7.6.1. Permanent Discontinuation of Study Treatment

If study treatment is permanently discontinued, the primary reason for permanent discontinuation of each study drug will be documented in the source documents and eCRF. Additional assessments following the end of treatment should be completed per Table 4 or Table 5.

Reasons for permanent discontinuation of study treatment may include:

- Adverse event that may jeopardize patient safety if the patient continues study treatment
- Patient noncompliance, defined as failure to comply with protocol requirements as determined by the investigator or sponsor
- Requirement or initiation of another, nonprotocol anticancer therapy
- Radiographically progressive disease per RECIST v1.1
  - Patients who are treated beyond initial radiographic disease progression, per the criteria outlined in Section 9.4.1, will be discontinued from study treatment upon subsequent radiographic disease progression per RECIST v1.1.
- Pregnancy
- Death
- Patient decision
- Physician decision
- Lost to follow-up
- Site or study termination
- Completion of maximum treatment duration of 2 years for quemliclustat/placebo after C1D1
- The patient's treatment assignment to quemliclustat or placebo has been unblinded and therefore quemliclustat or placebo will be discontinued. Patients may be allowed to continue with NP-Gem if permitted as described in Section 7.5.1.

Note that discontinuation from study treatment is NOT the same as withdrawal from the study. Patients discontinuing study treatment should proceed to follow-up assessments as outlined in Table 4 and Table 5.

Every effort must be made to ensure that protocol-specified follow-up procedures (as outlined in Table 4 and Table 5) are completed, unless patient also withdraws from noninterventional study procedures.

Upon discontinuation of study treatment, there are three options:

1. Continue with interventional study assessments (eg, radiographic assessments, questionnaires, physical exams, blood draws) and noninterventional study assessments (eg, medical record review, survival contacts by phone call), or
2. Withdrawal from interventional study assessments, but continue with noninterventional study assessments, or
3. Withdrawal from both interventional and noninterventional study assessments.

Patients may decide to partially withdraw from interventional study but agree to continue to be followed for noninterventional study assessments. Such cases would not be considered protocol deviations and should be documented in the study file.

Any requests for withdrawal from LTFU should be documented in source documents with investigator signature. In such instances, public information sources (eg, county records) will be used to obtain information about survival status, where allowed by country- and local-specific regulations.

7.6.2. Patient Discontinuation/Withdrawal from the Study

Individual patients may be discontinued from the study at any time the following reasons:

- Withdrawal of informed consent
- Death from any cause
- Lost to follow-up
- Site or study termination

The primary reason for withdrawal from study will be documented on the source documents and recorded on the appropriate eCRF.

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

For patients who remain alive at the time they are discontinued from the study, including withdrawal of consent, determination of survival status per public records (such as government vital statistics, obituaries, or third-party vendor records) will be performed where allowed by country- and local-specific regulations.

7.6.3. Screen Failure

A screen failure occurs when a patient consents to participate in the clinical trial but does not satisfy eligibility requirements within the screening (or rescreening) window and is not randomized.

If a patient does not satisfy any of the eligibility requirements during the initial screening assessment, any relevant assessment(s) may be repeated as needed during the screening window (Day -28 to Day 0) and prior to submission of the patient's eligibility to the sponsor. Otherwise, the patient will be considered a screen failure. An individual patient may be rescreened only once following authorization from the sponsor medical monitor or their designee. A patient who is rescreened will not be assigned a new patient identification number. Patients who are rescreened are not required to sign another ICF if the originally signed consent is still the current version. If a new ICF version exists at the time of rescreening, reconsent is required.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, and any SAE resulting from a screening-related procedure.

7.6.4. Lost to Follow-Up

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (at least 3 attempts by a combination of phone calls, text messages, email messages, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's source documents. If the patient does not respond within 1 month after the third contact, the patient will be considered lost to follow-up.
- For patients who are considered lost to follow-up prior to completion of all protocol-required study assessments presented in Table 4 or Table 5, the investigator will search for survival status via publicly available records (where permitted by country and local laws and regulations) per the regularly scheduled survival follow-ups shown in Table 4 or Table 5.

8. STUDY DRUG MATERIALS AND MANAGEMENT

The quemliclustat drug product is a sterile lyophilized powder for solution for injection, packaged in a glass vial. Refer to the respective product information for nab-paclitaxel and gemcitabine for a description of drug product and packaging.

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

Only patients enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

Refer to the Pharmacy Manual for details regarding preparation, handling, and storage of quemliclustat/placebo and to the approved prescribing information for NP and Gem.

9. ASSESSMENT OF EFFICACY

9.1. Overall Survival

Survival status will be monitored throughout the study as shown in Table 4 and Table 5. Survival follow-up may be collected via telephone calls, patient medical records, and/or clinic visits. For patients who discontinue from the study, including withdrawal of consent, determination of survival status via public records (such as government vital statistics, obituaries, or third-party vendor) will be performed where allowed by country- and local-specific regulations.

Details on the analysis of OS is provided in Section 11.4.1.1.

9.2. Subsequent Anticancer Therapy

Following discontinuation of study treatments, patients will be contacted Q6W in SFU/LTFU regarding subsequent anticancer treatment (systemic and nonsystemic) as shown in Table 4 and Table 5 until the patient is discontinued from the study per Section 7.6.2 Assessment of subsequent anticancer treatment can be collected via telephone calls, patient medical records, and/or clinic visits.

9.3. Assessment of Subsequent Radiographic Disease Progression for PFS-2

Progression-free survival-2 will be evaluated in the current study. In order to perform this analysis, assessment of subsequent radiographic disease progression will be assessed Q6W in SFU/LTFU as shown in Table 4 and Table 5. Subsequent PFS-2 related radiographic disease progression will begin after occurrence of radiographic progressive disease per RECIST v1.1 since randomization, using the previous radiographic progression as reference. For patients who are treated beyond initial radiographic disease progression, as described in Section 9.4.1, subsequent PFS-2 related radiographic disease progression will begin after the patients second radiographic disease progression since randomization or end of treatment, whichever occurs first, using the previous radiographic progression as reference. In all cases, the assessment of subsequent PFS-2 related radiographic disease progression will be performed until the patient is discontinued from the study per Section 7.6.2.

The assessment of subsequent radiographic disease progression will be based upon local standard clinical practice and therefore formal RECIST v1.1 assessment will not be required. The following data should be utilized to determine subsequent radiographic disease progression in order of priority and availability:

1. Investigator assessment of radiographic scans if the investigator continues to have access to a patient's subsequent imaging performed outside of this study.
2. Information available in the site's electronic medical record system, such as a radiology or clinical report, documenting radiographic disease progression.
3. Site contacts the patient to determine if the patient has experienced radiographic disease progression per their treating oncologist.

For each assessment, the date of the protocol specified timepoint, the patient's most recent imaging date and associated progression status (progressed, non-progressed, no new imaging since last contact) will be documented in the appropriate eCRF.

9.4. Disease Response Assessment

Imaging to assess disease response will be performed every 8 weeks through Cycle 12 and then once every 12 weeks (Q12W), as described in the SOA (Table 4 and Table 5). Note: Imaging is independent of study cycle and is based on calendar starting from the first dose. Additional disease assessments can be performed at any time during the study if deemed necessary by the investigator. Disease response assessment will be based upon investigator assessment using RECIST v1.1 criteria:

- If a disease response assessment performed as part of standard-of-care occurred prior to obtaining informed consent and within 28 days prior to randomization, the baseline disease assessment at Screening does not need to be repeated.
- Imaging modality for screening and on-study disease assessments:
  - Chest/abdomen/pelvis: CT scan should be performed or MRI if CT is not available, either one with oral/IV contrast unless contraindicated. If CT contrast is medically contraindicated, a noncontrast CT of the chest plus an MRI (preferably with contrast) of the abdomen and pelvis should be performed.
  - Brain imaging: MRI (preferred) or CT scan with contrast if a brain MRI is contraindicated or logistically not feasible.
  - If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
  - The same radiographic procedures used to assess disease sites at Screening should be used for all subsequent tumor assessments.
- Screening disease assessments will include chest/abdomen/pelvis. Imaging of the brain is only required if clinically indicated based upon signs/symptoms of brain metastases. All measurable and nonmeasurable lesions must be assessed and documented at screening.
- On-study disease assessments will include chest/abdomen/pelvis. Brain imaging will be performed as clinically indicated. All measurable and nonmeasurable lesions identified at screening and any new lesions must be followed, assessed, and documented.
- Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

- Patients who discontinue treatment for reasons other than radiographic progressive disease will continue disease assessment at the interval described in Table 4 and Table 5 until death, radiographic disease progression, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, or study termination, whichever occurs first. Patients treated beyond initial progression will continue disease assessments until a second radiographic disease progression per RECIST v1.1, treatment discontinuation, death, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, or study termination, whichever occurs first.

9.4.1. Treatment Beyond Initial Radiographic Disease Progression as per RECIST v1.1

Antitumor response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents. There is clinical evidence that patients treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. Some hypotheses have been put forth to explain this phenomenon. One hypothesis is enhanced inflammation within tumors leads to an increase in tumor size, followed by a decrease in the mass of both the malignant and inflammatory portions of the mass. The kinetics of the tumor may initially outpace antitumor activity in some patients and with sufficient time, the antitumor activity will dominate and become clinically apparent. Therefore, patients will be allowed to continue the study therapy after initial investigator-assessed RECIST v1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study treatment (Nishino, 2016; Yamaura, 2018; Jia, 2019; Mönch, 2023).

After the RECIST v1.1 criteria for initial radiographic disease progression are met (Appendix 4), a patient may be allowed to continue treatment if they meet all of the following criteria:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating progressive disease (ie, patient is clinically stable per investigator judgment).
- No decline in ECOG PS attributed to underlying malignancy.
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.
- Patient provides written informed consent acknowledging treatment beyond progression using a designated ICF prior to receiving additional study treatment.

The decision to continue study treatment after initial radiographic disease progression per RECIST v1.1 is at the discretion of the investigator and requires that the patient agree to this treatment plan, and that the shared decision to treat beyond initial radiographic progression is documented.

Patients who continue treatment beyond initial radiographic disease progression per RECIST v1.1 will be discontinued from treatment if radiographic disease progression is confirmed by the investigator per RECIST v1.1 at the next scheduled disease assessment, no sooner than 4 weeks from the previous assessment of radiographic progressive disease.

9.5. Patient-Reported Outcomes

Patients will be asked to complete the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Pancreatic Cancer Module (QLQ-PAN26), EORTC Quality of Life Questionnaire-Core 30 Version 3 (QLQ-C30), and 5-Level EuroQol-5 Dimensions (EQ-5D-5L) questionnaires at the timepoints listed in Table 4 and Table 5. When questionnaires are to be completed, they will be completed at the beginning of each visit day before any clinical activities are performed. Questionnaires will be provided in the patient's preferred language, if available.

Patient-reported outcomes translated into the patient's preferred language must be completed at the C1D1 visit and throughout the study period, as listed in Table 4 and Table 5. If the translated version(s) of any PRO are not available in the preferred language at the patient's C1D1 visit and therefore cannot be completed by the patient at C1D1, then the untranslated PRO(s) will not be required for this patient at any point during their study participation.

9.5.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3 (EORTC QLQ-C30)

The EORTC QLQ-C30 is a reliable and valid measure of PRO and has been widely used among cancer patients. The EORTC QLQ-C30 includes 30 separate positions (items) resulting in five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), one global health status scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week).

9.5.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer Module (EORTC QLQ-PAN26)

The EORTC QLQ-PAN26 is a PRO instrument that measures quality of life for people with pancreatic cancer, focusing on disease symptoms, treatment side effects, and emotional issues specific to pancreatic cancer. It has completed all three instrument development phases laid out by EORTC. The EORTC QLQ-PAN26 includes 26 separate items assessing pancreatic- and treatment-related symptoms (pain, digestive, cachexia, altered bowel habit, hepatic symptoms, side effects, ascites, indigestion, and flatulence) and emotional domains (body image, healthcare satisfaction, sexuality, fear of future health, and ability to plan for the future). The recall period is 1 week (the past week).

9.5.3. 5-Level EuroQol-5 Dimension (EQ-5D-5L)

The EQ-5D-5L is an established generic quality-of-life instrument that measures 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with each dimension having a 5-level response option. There is also a visual analogue scale (0 to 100) to measure overall health. The recall period for all questions is the day the questionnaire is completed ("Today").

10. STUDY ASSESSMENTS

Planned timepoints for all study assessments are provided in the SOA (Table 4 and Table 5).

10.1. Safety Parameters

10.1.1. Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure (while the patient is in a seated position), temperature, and pulse oximetry. Vital signs should be measured at the specified study visits outlined in the SOA (Table 4 and Table 5) and as clinically indicated throughout study treatment.

10.1.2. Physical Examination

A complete physical examination will be performed at Screening and C1D1. A complete physical examination will include, at a minimum, assessments of general appearance, examination of the skin, head, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Any clinically significant abnormality identified prior to the first dose of study treatment should be recorded in the patient's source documentation and entered on the appropriate medical history eCRF unless considered an SAE related to a screening procedure. In addition, all new abnormalities must be assessed as clinically significant or not clinically significant by a qualified investigator, and these assessments must be documented in the source documentation. A symptom-directed physical examination will be conducted at all other specified timepoints. Height, weight, and body surface area will also be measured and recorded at timepoints detailed in the SOA (Table 4 and Table 5) and as clinically indicated throughout study treatment.

10.1.3. Electrocardiogram

Triplicate 12-lead ECG recordings are required at screening and as clinically indicated throughout study treatment. The three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

Circumstances that may induce changes in heart rate, including environmental distractions (eg, television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording. Prior to an ECG recording, patients must rest in a supine or semi recumbent position for at least 5 minutes. Lead placement should be as consistent as possible for each ECG recording.

All ECGs will be read locally and ECG parameters including clinical interpretation will be documented. For safety monitoring purposes, the investigator or qualified designee must document review of all ECG tracings and document whether any abnormalities are clinically significant or not clinically significant. Any clinically significant ECG abnormalities must be documented and recorded as an AE.

10.1.4. Laboratory Assessments

A list of clinical safety laboratory tests (hematology, coagulation, serum/plasma chemistry) to be performed in this study and where they are being analyzed is provided in Appendix 3 at the timepoints shown in the SOA (Table 4 and Table 5).

The investigator or a qualified designee must review the laboratory report, assess the clinical significance of any out-of-range values, document this review and the assessments of clinical significance, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significant abnormal during participation in the study should be repeated until the values return to Grade ≤ 1 or baseline or are no longer considered clinically significant by the investigator or Medical Monitor (or their designee).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded. In addition, the lab normal range should also be collected.

10.1.5. Pregnancy Screen

Pregnancy testing will be performed by obtaining serum (from whole blood) or urine samples at study visits indicated in the SOA (Table 4 and Table 5) for women of child-bearing potential only. At Screening and prior to dosing on C1D1, pregnancy testing will be performed on serum samples. For all other visits where pregnancy testing is required, a urine pregnancy test will be conducted (unless serum test is preferred per site practice). If results of the urine test are ambiguous, a serum test must be conducted to confirm pregnancy status. Testing must be repeated until the result is unambiguous. Results must be reviewed prior to dosing. In the event of a patient becoming pregnant or a patient's partner becoming pregnant, refer to Section 10.4.10 for pregnancy reporting requirements.

10.1.6. Eastern Cooperative Oncology Group Performance Status

Patients' ECOG PS will be assessed at study visits detailed in the SOA (Table 4 and Table 5) using the grading scale in Table 13.

Table 13: Eastern Cooperative Oncology Group (ECOG) Grading Scale

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

10.2. Pharmacokinetics

Blood samples for PK analyses will be collected from patients according to the SOA in Table 4 or Table 5, as applicable. In addition, specific timepoints for blood collection for quemliclustat can be found in patients as indicated in Table 4. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements, including shipping and storage conditions.

Table 14: Timepoints for Blood Sampling for Quemliclustat/Placebo Pharmacokinetics

Cycle	Day	Nominal Time	Collection Windows	Quemliclustat PK
Cycle 1	1	Predose		X
Cycle 1	1	End of infusion	+ 20 min	X
Cycle 2	1	Predose		X
Cycle 2	1	End of infusion	+ 20 min	X
Cycle 3	1	Predose		X
Cycle 4	1	Predose		X
Cycle 5	1	Predose		X
Cycle 6	1	Predose		X
Cycle 7	1	Predose		X
Cycle 11	1	Predose		X
Cycle 14	1	Predose		X
EOT		One sample drawn any time during visit[a]		X
SFU		One sample drawn any time during visit		X

AB680 = quemliclustat; EOT = end of treatment; min = minute; PK = pharmacokinetics; SFU = Safety Follow-Up
[a] This sample should be taken before the patient has started subsequent treatment (systemic, radiation, or surgery).

10.3. Biological Samples for Biomarker Analysis

10.3.1. Tumor Tissue Sample for Exploratory Biomarker Analysis

If available, archival tumor tissue sample must be provided for future tumor biomarker analysis which may include, but is not limited to, testing through immunohistochemistry and sequencing RNA and DNA. The expression of one or more proteins (eg, CD73) and expression of one or more genes or gene signatures will be explored. If archival tissue sample is not available, a new biopsy is not required.

The most recent archival tumor samples will be obtained at screening for exploratory biomarker analyses, including, but not limited to, the target (CD73) expression through immunohistochemistry and sequencing of RNA and DNA. A formalin-fixed, paraffin-embedded (FFPE) block is the preferred sample type. If an FFPE block cannot be submitted, then a set of fresh cut slides (minimum of 10 slides) may be provided. If fresh cut slides are not possible, the most recent archival unstained slides may be submitted for testing.

All assessments will be performed in accordance with country-specific regulations.

10.3.2. Blood Samples for Exploratory Biomarker Analysis

Blood samples will be collected according to Table 4 and Table 5 from all eligible patients for analyses of tumor- and immune-associated protein and DNA/RNA biomarkers present in blood. An exploratory objective of this study is to assess changes in tumor- or immune-related biomarkers in blood that may provide evidence for biological activity of the quemliclustat plus NP-Gem over placebo plus NP-Gem.

Refer to the central laboratory manual for sample collection requirements, including shipping and storage conditions.

Because biomarker science is a rapidly evolving area of investigation, sample collection and analysis may be modified during the study at the discretion of the sponsor based on new state-of-the-art scientific knowledge.

Blood and tissue samples will be collected and stored in accordance with applicable law for research purposes and may be used for future research. Samples may be sent to one or more central laboratories, collaborators, or research partners of the sponsor. Analysis may be performed by the sponsor or sponsor's designee to contribute to the understanding of the disease biology, the development of related or new treatments. Some of the samples collected for biomarker analyses may also be used for developing future diagnostic tests by the sponsor or its designated partners. Samples not analyzed during study conduct may be stored for up to fifteen (15) years or as long as country-specific regulations allow after the end of the main study.

10.3.3. Biomarker Samples for Future Research

The remainder of the biomarker specimens and/or PK samples already collected may be used to advance knowledge of the disease biology or development of the study drugs, unless prohibited by country law, regulation, and/or central/local Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. Future research may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for personalized treatment of patients in the future.

10.4. Adverse and Serious Adverse Events, and Special Situation Reporting

10.4.1. Definitions

10.4.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, invasive screening procedures such as biopsies)

10.4.1.2. Serious Adverse Events

An SAE is an AE occurring at any dose of the investigational product, comparator, or placebo, that fulfills 1 or more of the following:

- It results in death
- It is immediately life-threatening (ie, the AE, in the view of the investigator, places the patient at immediate risk of death)
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital anomaly or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

10.4.1.3. Special Situations

Special situations include exposure during pregnancy, medication errors, and misuse or abuse of the investigational product.

Medication error is any unintended failure in the drug treatment process (ie, the prescribing, dispensing, preparation for administration, or administration of a study drug while the medication is in the control of the healthcare provider, patient, or consumer) that leads to or has the potential to lead to patient harm.

Misuse is the intentional and inappropriate use of the medicinal product that is not in accordance with the protocol instructions or local prescribing information.

Abuse is the persistent or sporadic, intentional, excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

10.4.1.4. Events Not Qualifying as an Adverse Event

An event that is part of the natural course of the disease under study (ie, disease progression, death due to disease progression) should not be recorded as an AE or SAE term. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

All deaths that occur while on study will be recorded on the appropriate eCRF.

10.4.2. Classifications

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe, or according to the NCI CTCAE v5.0; see Section 10.4.4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious adverse events are required to be reported by the investigator or designee to the sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 10.4.5 for reporting instructions).

10.4.3. Assessment of Causality

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to study treatment, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration (Table 15).

For patients receiving combination treatment, causality will be assessed individually for each protocol mandated therapy.

Table 15: Causal Attribution Guidance

Is the AE suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study treatment; and/or the AE abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge. "Related" means that the event is at least possibly related to study treatment.
NO	Evidence exists that the AE has an etiology other than study treatment (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of study treatment (eg, cancer diagnosed 2 days after first dose of study treatment). "Unrelated" means that the event is unlikely related to study treatment.

AE = adverse event.

10.4.4. Assessment of Severity

The investigator is responsible for assessing the severity of each AE reported during the study using NCI CTCAE v5.0.

Table 16 provides guidance to be used for assessment of AE severity for events not listed in the NCI CTCAE v5.0.

Table 16: Adverse Event Severity Grading Scale for Events Not Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b, c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to AE[d]

AE = adverse event; NCI CTCAE (v5.0) = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE (see Section 10.4.5 for reporting instructions), per the definition of a SAE in Section 10.4.1.2.

[d] Grade 4 and 5 events must be reported as SAE (see Section 10.4.5 for reporting instructions) should the event meet the definition of SAE in Section 10.4.1.2.

10.4.5. Reporting Adverse Events

The investigator is responsible for ensuring that all AEs are recorded in the patient's source documentation and entered on the AE eCRF and reported to the sponsor in accordance with instructions provided in this section.

10.4.5.1. Adverse Event Reporting Period

The time periods for collection of AE, SAE, and special situation reportable safety event information for this protocol are defined in Table 17. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent in accordance with the specified time periods.

Table 17: Time Period for Collecting AE, SAE, and Special Situation Safety Event Information

Reportable Safety Event	Time Period[a]
AEs related to a protocol mandated procedure and all SAEs[b]	Signed informed consent until first dose of study intervention
AEs/SAEs	From the first dose of study intervention until 30 days after the last dose of study treatment or until initiation of a new systemic anticancer therapy, whichever occurs first.
Pregnancy in female partner of a study patient or a study patient	From the first dose of study intervention until 6 months after the last dose of NP-Gem, or 30 days after the last dose of quemliclustat or longer if required by local regulations, whichever is longest.
Overdose, medication errors, misuse, and abuse	From the first dose of study intervention through completion of study intervention

AE = adverse event; eCRF = electronic case report form; NP-Gem = nab-paclitaxel and gemcitabine; SAE = serious adverse event

[a] Investigators are not obligated to actively seek AE or SAE information after the end of the reporting period. However, if the investigator learns of any SAE, including a death, at any time after the end of the reporting period, and he/she considers the event to be reasonably related to study treatment or study participation, the event should be promptly reported to the sponsor or its designee according to Section 10.4.5. Every effort should be made to follow AEs and SAEs considered related to study treatment or protocol-related procedures until a final outcome can be reported.

[b] Other clinically relevant medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history eCRF.

10.4.6. Procedure for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs in the source documentation and entering them on the AE eCRF. Only one AE term should be recorded in the event field on the AE eCRF.

10.4.6.1. Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs/SAEs based on signs and symptoms should be nullified and replaced by one AE/SAE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first sign or symptom of the eventual diagnosis.

10.4.6.2. Deaths

For this protocol, mortality is an efficacy endpoint. All deaths that occur during the reporting period, regardless of relationship to study treatment, must be recorded on the appropriate eCRF immediately. Furthermore, if a death meets SAE criteria, it must be reported in an expedited manner to the sponsor per Section 10.4.7.

10.4.6.3. Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an AE or SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (eg, for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not experienced an AE related to the preexisting condition.
- Hospitalization due solely to the progression of the underlying cancer.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

10.4.7. Events Requiring Expedited Reporting to Sponsor

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator becomes aware of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours of becoming aware of the event, regardless of relationship to investigational product:

- All SAEs (defined in Section 10.4.1.2)
- Pregnancies (see Section 10.4.10 for details on reporting requirements)
- Overdose (defined in Section 7.2.3) and other special situations (ie, medication errors, misuse, abuse). Report via the SAE form (see Section 10.4.8).

The investigator must report new significant follow-up information for these events to the sponsor immediately (ie, no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis

- Significant new diagnostic test result
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

10.4.8. Serious Adverse Event Reporting Requirements

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to the sponsor no more than 24 hours after site personnel become aware of the event. Any follow-up information on a previously reported SAE will also be reported to the sponsor no more than 24 hours after becoming aware of the new information.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.4.3.

Primary SAE Reporting Method:

Serious adverse events will be reported to the sponsor within 24 hours of the knowledge of the event via entry on the AE eCRF and associated eCRFs, which will be completed and submitted to the clinical database via the electronic data capture (EDC). If electronic reporting is unavailable via the eCRFs, the investigator will complete an SAE form and submit it by email/fax as described below.

Email: safety@arcusbio.com

Fax: Refer to the SAE form for region-specific numbers. Fax should only be utilized if email is unavailable.

Emergency Medical Contact

Arcus Biosciences, Inc. Medical Monitor contact information:	
Contact information:	medicalmonitor-prism-1@arcusbio.com
Telephone number:	+1 (510) 999-5887

Alternate/Regional medical monitor contact information is provided in the investigator site file.

10.4.9. Regulatory Reporting Requirements

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an investigational product under clinical investigation are met. Investigators must also comply with local requirements for reporting SAEs to the IRB/IEC or other local health authorities.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The sponsor will promptly evaluate all SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to relevant health authorities based

on applicable legislation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Upon receipt of a suspected unexpected serious adverse reaction (SUSAR) report from the sponsor or designee, the investigator must comply with all applicable requirements related to the reporting of SUSARs per institutional guidelines.

10.4.10. Collection of Pregnancy Information

The investigator will attempt to collect pregnancy information on any female patient or any male patient's female partner who becomes pregnant during the course of study participation. Monitoring of the mother should continue until the conclusion of the pregnancy. The newborn should be monitored for up to 12 weeks (or longer if required by local law/regulation) for a healthy newborn or at least 1 year for a newborn with complications.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the Pregnancy Report Form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. Follow-up information on the status of the mother (female patient or male patient's female partner) and child will be forwarded to the sponsor by updating the Pregnancy Report Form. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

In addition, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported on the AE eCRF and associated eCRFs and electronically submitted in the clinical database.

10.4.11. Adverse Events of Special Interest

No adverse events of special interest (AESIs) have been defined for this study. All AEs and SAEs should be reported as described in Section 10.4.6 and Section 10.4.8.

10.4.12. Protocol-Specific Events That Qualify as Serious Adverse Events

All laboratory abnormalities meeting Hy's Law case criteria, defined below, qualify as SAEs and must be reported as per Section 10.4.1.2.

Patients meeting the following criteria will meet Hy's Law case criteria:

- Alanine aminotransferase or AST > 3 × ULN concurrent with serum total bilirubin > 2 × ULN and serum alkaline phosphatase < 2 × ULN; and,
- No other reason is found to explain the combination of increased ALT/AST and serum total bilirubin, such as evidence of new or worsening liver disease/metastasis, preexisting liver disease, viral hepatitis, alcohol abuse, ischemia, or another drug capable of causing the observed injury.

11. STATISTICAL CONSIDERATIONS

This section is intended to provide an overview of the planned statistical analyses for this study. Further details of statistical methods and data handling will be provided in a separate statistical analysis plan (SAP), which will be finalized prior to the planned interim analysis of the primary endpoint. Any deviation from analyses in the SAP will be described in the Clinical Study Report.

11.1. Statistical Hypotheses

The primary efficacy endpoint is OS in the intent-to-treat (ITT) population. The null (Hø) and alternative (Ha) hypotheses regarding OS can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ for Arm A (quemliclustat + NP-Gem) and Arm B (Placebo + NP-Gem), respectively:

$$H\text{ø}: S_A(t) = S_B(t) \text{ versus } Ha: S_A(t) > S_B(t)$$

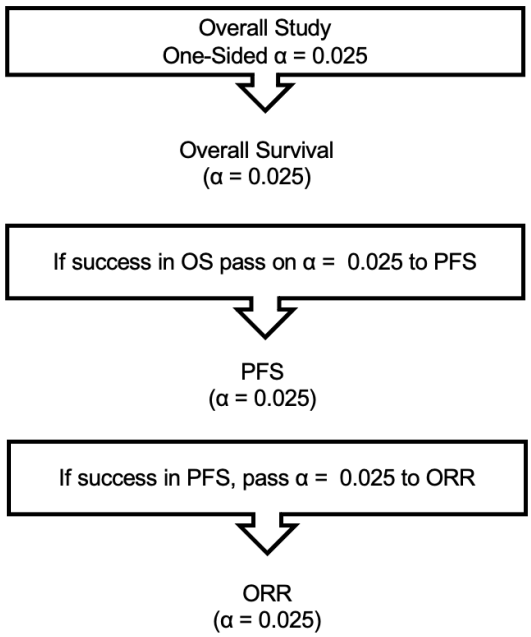
11.1.1. Multiplicity Adjustment and Type I Error Control

The overall type I error (α) of this study is 0.025 (1-sided). To control the overall type I error, the statistical comparisons for the primary efficacy endpoint of OS and the secondary efficacy endpoint of PFS and ORR will be carried out in the hierarchical order with alpha allocation (Burman, 2009) as indicated in Figure 2.

Statistical significance for OS is required to initiate testing of the secondary endpoints. Each test will be performed at a one-sided significance level of 0.025.

If the PFS comparison between Arm A and Arm B is statistically significant at the one-sided alpha level of 0.025, ORR will be tested at the overall one-sided alpha level of 0.025. If ORR is statistically significant, testing of other endpoints may be performed and will be detailed in the SAP.

Figure 2: Overall Type I Error Control Strategy



ORR = objective response rate; OS = overall survival; PFS = progression-free survival

11.2. Sample Size Determination

The sample size is based on the number of OS events for the superiority test of the primary efficacy endpoint of OS for Arm A (quemliclustat + NP-Gem) versus Arm B (placebo + NP-Gem). Eligible patients will be randomized in a 2:1 ratio to two treatment arms: Arm A and Arm B. Randomization will be stratified by liver metastases (present versus absent), ECOG PS (0 versus 1), and region (North America and Western Europe versus East Asia versus Rest of World).

A total of 446 OS events are required to achieve 90% statistical power to detect a statistically significant treatment difference in OS between Arm A and Arm B, based on the following assumptions:

- Overall one-sided alpha of 0.025
- Target HR of 0.724, corresponding to an improvement in median OS from 9.2 months to 12.7 months (increase by 3.5 months)
- One interim analysis with information fraction of 85%
- Lan-De Mets approximation of O'Brien-Fleming spending function (DeMets and Lan, 1994) to control the overall Type I error rate of the interim and final analyses

Approximately 610 patients will be enrolled and randomized in a 2:1 ratio to Arm A and Arm B within approximately 24 months. With the assumption of a 5% annual dropout rate for OS, a total of 446 OS events are expected to be observed approximately 41 months after the first patient is randomized.

11.3. Analysis Populations

The populations for analysis are defined in Table 18.

Table 18: Analysis Populations

Analysis Set	Description
ITT Population	All patients who are randomized. Treatment arms will be compared based on randomized treatment, regardless of the treatment received, following the "intent-to-treat" principle.
Safety Population	All patients who are randomized and receive any amount of study drug.
Pharmacokinetic Evaluable Population	All patients who receive at least 1 dose of quemliclustat and for whom pharmacokinetic data are considered interpretable and analyzable.
Biomarker Evaluable Population	All patients who receive any study drug with interpretable and analyzable biomarker data.

ITT = intent-to-treat

Efficacy analyses will be performed in the ITT population whereas safety analyses will be performed in the Safety population. Additional analysis populations, such as PK and Biomarker evaluable populations may be utilized based on sample and data availability, as appropriate.

11.4. Efficacy Analyses

Efficacy analyses will be presented by treatment group in the ITT population as defined in Table 18. Tumor response evaluations will be assessed by investigators according to RECIST v1.1.

11.4.1. Primary Efficacy Endpoint

11.4.1.1. Overall Survival

The primary efficacy endpoint of OS is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of the analysis will be censored at the last date they were known to be alive using all relevant dates available in the database. Patients with no available data after randomization will be censored at the date of randomization.

Overall survival will be compared between treatment groups using a stratified log-rank test in the ITT population. The hazard ratio and 95% confidence interval (CI) will be estimated using a stratified Cox regression model, with ties handled using Efron's approximation method (Efron, 1977) and CI calculated using Wald's confidence limits. The stratification factors for the log-rank test and Cox regression will be those used for randomization stratification (liver metastasis at baseline [present versus absent], ECOG performance score at baseline [0 versus 1], and region [North America and Western Europe versus East Asia versus Rest of World]). In the situation where there is insufficient information in a stratum, pooling of the stratum with the smallest adjacent stratum for stratified analyses will be considered.

Kaplan-Meier estimates of median OS, first and third quartiles of OS, and the OS rates at 6, 12, and 18 months will be presented by treatment arm, and the respective 95% CIs will be based on the log-log transformation of the survival function. The 95% CIs for OS quartiles and OS rates will be constructed using Brookmeyer-Crowley method (Brookmeyer, 1982) and Greenwood's formula respectively.

11.4.2. Secondary Efficacy Endpoints

11.4.2.1. Progression-Free Survival

The secondary endpoint of PFS as assessed by the investigator according to RECIST v1.1 is defined as the time from the date of randomization until first documentation of progressive disease or death from any cause, whichever occurs first. Patients without documented disease progression who are still alive at the time of analysis will be censored as shown in Table 19.

Table 19: Events and Censoring Scheme for PFS and DOR

Situation	Analysis
No adequate post-baseline tumor assessment and no death*	Censored at date of randomization
No PD, no death, and no new anticancer treatment initiated	Censored at last adequate tumor assessment
No PD and no death; new anticancer treatment is initiated	Censored at last adequate tumor assessment before new anticancer treatment
New anticancer treatment initiated prior to PD or death	Censored at last adequate tumor assessment before new anticancer treatment
PD or death documented after ≥ 2 missed tumor assessments	Censored at last adequate tumor assessment prior to the ≥ 2 missed tumor assessment
PD or death documented after ≤ 1 missed tumor assessment	Progressed at date of documented PD or death

DOR = duration of response; PD = progressive disease; PFS = progression-free survival
*Only applicable to PFS.

The time to event analysis methods described for the primary endpoint of OS (Section 11.4.1) will be applied to the secondary endpoint of PFS.

11.4.2.2. Objective Response Rate

The ORR is defined as the proportion of patients who have achieved best overall response of confirmed complete response (CR) or partial response (PR) as assessed by the investigator according to RECIST v1.1. Patients not meeting the criteria of confirmed CR or PR, or who discontinue before obtaining postbaseline tumor assessments will be considered non-responders. For each treatment arm, an estimate of ORR will be presented along with its corresponding exact binomial Clopper-Pearson 95% CI. The Cochran-Mantel-Haenszel method (Cochran, 1954; Mantel and Haenszel, 1959) will be used for comparison of the ORR between the treatment arms and to construct the 95% CI of the differences in ORR. The stratification factors will be the same as those used for randomization.

11.4.2.3. Duration of Response

Duration of response (DOR) is defined as the time from the first objective response (CR or PR) as assessed by investigator, per RECIST v1.1 to first documentation of progressive disease or death due to any cause, whichever occurs first. The DOR will be summarized descriptively using the Kaplan-Meier method and only patients who achieve a confirmed CR or PR will be included in this analysis. Responders without documented disease progression who are still alive at the time of analysis will be censored as shown in Table 19.

The time to event analysis methods described for the primary endpoint of OS (Section 11.4.1) will be applied to the secondary endpoint of DOR.

11.4.2.4. Disease Control Rate

Disease control rate (DCR) will be measured by the percentage of patients with a best overall confirmed response of CR, confirmed PR, or stable disease according to RECIST v1.1. The minimum criterion for stable disease duration is 8 weeks from randomization. The analysis methods described for ORR (Section 11.4.2.2) will be applied to DCR.

11.4.3. Handling of Missing Data

In the analysis of OS, patients without a documented death at the time of the analysis will be censored at the last date they were known to be alive. Patients with no postbaseline information will be censored on the date of randomization.

In the analysis of PFS, patients without documented disease progression or death at the time of analysis will be censored on the date of their last tumor assessment. Patients with no postbaseline tumor assessments will be censored on the date of randomization.

In the analysis of ORR, patients without postbaseline tumor assessments will be considered non-responders.

11.4.4. Subgroup Analyses

Subgroup analyses of the primary (OS) and secondary endpoints (PFS and ORR) will be conducted to assess consistency of treatment effect across the following subgroups:

- Stratification Factor: Liver metastasis (present, absent)
- Stratification Factor: ECOG PS at baseline (0, 1)
- Stratification Factor: Region (North America and Western Europe, East Asia, Rest of World)
- Age (< 65, ≥ 65)
- Sex (female, male)
- Race/ethnicity (Asian, non-Asian)
- Prior antipancreatic cancer surgery (yes, no)

Details of these subgroup analyses will be provided in the SAP and additional subgroup analyses may also be specified in the SAP.

11.5. Safety Analysis

Safety analyses will be based on the Safety population, as defined in Table 18. Duration of treatment and relative dose intensity of study drugs will be summarized descriptively by treatment group. The incidence of TEAEs will be summarized by treatment group. Clinically meaningful trends in other safety parameters, such as clinical laboratory parameters, vital signs, and ECGs may also be summarized descriptively by treatment group.

11.5.1. Extent of Exposure

Treatment duration and relative dose intensity of study drugs will be summarized by treatment group.

Treatment duration and relative dose intensity are defined as below:

- Treatment duration (months) = (date of last dose – date of first dose + 1)/30.4375
- Relative dose intensity (%) = (total amount of study drug received[1]/total amount of study drug planned per protocol)[2] × 100

[1] Total drug received will be the sum of doses received.

[2] Total dose planned per protocol will be calculated as follows:

planned dose level * [last dosing date of the corresponding study drug – first dosing date of the corresponding study drug + X] / X, where X is the planned dose interval in days.

11.5.2. Adverse Events

Treatment-emergent adverse events are AEs occurring between the first dose date and the end of the AE collection period or the initiation of a new anticancer therapy, whichever occurs first. Verbatim descriptions of AEs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities, and AEs will be graded according to the NCI CTCAE v5.0.

The incidence of TEAEs will be summarized with severity, causality, seriousness, and action taken with study drug by treatment group. The number and percentage of patients with TEAEs in each treatment group will be presented by preferred term and/or system organ classes. A patient will be counted once at the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term are reported.

All AE data will be presented in a data listing, where TEAEs will be flagged. Serious AEs and TEAEs leading to discontinuation of study treatment will also be presented in separate data listings.

11.5.3. Clinical Laboratory Evaluations

Laboratory results will be graded according to NCI CTCAE as appropriate. Shifts in grade from baseline to worst postbaseline grade will be summarized for applicable laboratory parameters by treatment group. Abnormal laboratory findings will be presented in listings by laboratory panel.

11.6. Other Endpoint Analyses

11.6.1. Second Progression-Free Survival

The PFS-2 is defined as the time from the date of randomization until second progressive disease or death from any cause, whichever occurs first. Patients without second disease progression who are still alive at the time of analysis will be censored on the last date known alive.

The time to event analysis methods described for the primary endpoint of OS (Section 11.4.1) will be applied to PFS-2.

11.6.2. Pharmacokinetic Analyses

Pharmacokinetic analyses will be based on the PK evaluable population (Section 11.3). Individual concentration-time plots for quemliclustat may be presented for each patient as well as mean concentration-time plots for Arm A. A population PK analysis may also be performed by combining with PK data from other clinical studies to obtain PK parameters for quemliclustat; if performed, it will be reported separately.

11.6.3. Biomarker Analysis

The biomarker readout and relation to clinical activity may be summarized as warranted by the sample size.

The efficacy of study treatment may be correlated to exploratory biomarkers including but not limited to protein expression in the tumor tissue and other exploratory biomarkers in blood samples. In addition, potential correlations of these biomarkers with mechanism of action or resistance to drug regimen in different arms may be explored.

11.7. Interim Analysis

An interim analysis of the primary efficacy endpoint of OS in the ITT population will be performed when approximately 379 OS events have occurred in the ITT population. The analysis methods described in Section 11.4.1 will be applied to the interim analysis. Based on the statistical assumptions provided in Section 11.2 and expected number of events, the associated efficacy boundaries for the interim and final analyses of OS in the ITT population are estimated in Table 20. The Lan-DeMets approximation of O'Brien Fleming alpha spending function will be utilized to control the type I error for the interim and final analyses. The nominal alpha is estimated to be 0.015 and 0.0207 for the interim at 85% information fraction and at the final analyses, respectively.

Table 20: Number of Events, Statistical Power, and Efficacy Boundary of Interim and Final Analysis of Primary Endpoint (OS)

Analysis (Arm A vs Arm B)	Expected Events (% of Patients)	Nominal Alpha (1-sided)	Statistical Power	Efficacy Boundary in HR	Projected Analysis Time After FPI
Interim (85% IF)	379 (62%)	0.0151	80%	0.793	34 months
Final	446 (73%)	0.0207	90%	0.818	41 months

FPI = first patient in; HR = hazard ratio; IF = information fraction; OS = overall survival; vs = versus

Other efficacy and safety endpoints will also be analyzed at the interim analysis. The statistical comparisons for the secondary efficacy endpoints between treatment arms will be carried out in the hierarchical order as shown in Section 11.1.1.

An IDMC comprised of independent experts will review the interim efficacy analysis results to make recommendation on efficacy claim based on the interim efficacy results. In addition, the IDMC will routinely monitor accumulating safety data from the study to ensure patient safety. The composition and operating procedures of the IDMC will be detailed in the IDMC Charter.

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated to all investigators (for example, by phone and/or email) as soon as possible. Investigators are required to respond to confirm they understand the communication and have taken appropriate action prior to further dosing. The sponsor will follow-up with any investigator who has not responded prior to any further dosing. If a dose is planned imminently, the sponsor will immediately and continually follow up with the investigator until contact is made and instructions are verified.

12.2. Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

12.3. Data

The sponsor does not proactively share data from Phase 3 clinical trials. Requests for access to Phase 3 clinical data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data, as well as the nature of the data collected.

12.4. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Arcus will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator and other personnel their responsibilities regarding protocol adherence and the responsibilities of Arcus or its representatives. This will be documented in a Clinical Study Agreement between Arcus and the investigator.

During the study, a monitor from Arcus or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator.
- Confirm facilities remain acceptable.
- Confirm the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.

- Perform source data verification. This includes a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each study patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Arcus.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Arcus and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

12.5. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with his/her financial interests in and/or arrangements with the sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/sub-investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the sponsor. Investigators are responsible for providing information on financial interests before and during the course of the study and for 1 year after completion of the study.

12.6. Institutional Review Board/ Independent Ethics Committee

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations (eg, FDA regulations, European Union [EU] Clinical Trials Regulation [No 536/2014], etc.).

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, EU regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.7. Data Protection

Personal data are collected, stored, and transferred in compliance with relevant data protection laws and regulations. The sponsor maintains the confidentiality of personal data as described in the ICF, including by assigning a unique study-specific number to each patient enrolled in the study. This means that patient names and other directly identifying information are not provided to the sponsor or its service providers, except as needed for study monitoring or auditing purposes. The principal investigator and site staff will have access to the patient names and unique study specific numbers and will only provide that information to others as permitted in the ICF, a separate authorization, or as required by law. All entities having access to coded or uncoded patient personal data must have in place technical and organizational measures sufficient to prevent unauthorized access, disclosure, dissemination, alteration, or loss of the information.

Medical information may be given to appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study that includes directly identifying personal data, including the patient's name, must be available for inspection upon request by representatives of national and local health authorities, the sponsor, or its designee (for study monitoring or auditing purposes), and the IRB/IEC for each study site, as appropriate.

The sponsor maintains a data protection officer to oversee its handling of personal data. In case of a breach of personal data, the sponsor will take appropriate action, including, where required, notification to relevant data protection authorities and/or patients. The sponsor provides contact information in the ICF for patients to use in order to exercise their rights regarding their personal data.

The patient must be informed that his/her medical records may be examined by monitors or auditors appointed by the sponsor, or other appropriate medical personnel responsible for the patient's welfare, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 must also be explained to the patient who will be required to give consent for his/her data to be used as described in the informed consent.

The patient must be informed of his/her rights regarding his/her personal data as well as how to make contact regarding any questions or concerns associated with the handling of his/her personal data.

12.8. Study and Site Start and Closure

12.8.1. First Act of Recruitment

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

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

12.8.2. Study/Site Termination

The sponsor or 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 (by the sponsor or designee) or study site by the sponsor or investigator may include:

For study termination:

- Discontinuation of further study intervention development
- The incidence or severity of AEs in this or other studies indicate the potential hazard to patients
- Patient enrollment is unsatisfactory

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator

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) (CROs) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

12.9. Committee Structure

This study utilizes an IDMC to ensure the continued safety of patients in the study. Details for the IDMC are provided below and further in the IDMC Charter.

12.9.1. Independent Data Monitoring Committee

Data monitoring will be conducted by an external IDMC that will meet to review interim data from this clinical trial. The IDMC will consider the overall risk and benefit to trial patients and will make recommendations to the sponsor's Development Review Committee (DRC) Chair regarding steps required to ensure patient safety and the continued ethical integrity of the trial and if the trial should continue in accordance with the protocol.

The IDMC will be composed of members external to the sponsor. The members of the IDMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members of the IDMC and the sponsor protocol team, meeting facilitation, the trial governance structure, and requirements for and proper documentation of IDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the IDMC. The IDMC will monitor the trial at an appropriate frequency as described in the detailed IDMC charter. A detailed communication plan will also be included in the IDMC charter.

12.10. Dissemination of Clinical Study Data

All data generated in this study required to be publicly available will follow all local and global reporting requirements. Any request to delay submission of study results will follow the appropriate regulatory procedures, if warranted. Peer reviewed publication(s) of the study results will follow the publication policy detailed in Section 16.

12.11. Reporting Requirements for Serious Breaches

A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.

Prompt notification by the investigator to Arcus of any (potential) serious breach of the protocol, or regulations is essential so that legal and ethical obligations are met.

- In certain regions/countries, Arcus has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - Arcus will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, Arcus is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will promptly inform the appropriate Arcus representatives immediately after they become aware of it: dl-clinicalqa@arcusbio.com.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Data Quality Assurance

Sites will be responsible for data entry into the EDC system and will receive training for appropriate eCRF completion. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing 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.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

13.2. Audits and Inspections

Authorized representatives of Arcus, a regulatory authority, an IEC, or an IRB will visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH, and GCP guidelines and any applicable regulatory requirements. The investigator should contact Arcus immediately if contacted by a regulatory agency about an inspection.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Arcus before he or she can enroll any study patients.

The investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit study patients. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Arcus will provide this information to the investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP, other applicable regulatory requirements, and the Arcus policy on Bioethics.

14.3. Written Informed Consent

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before any study-specific screening procedures were performed. The authorized person obtaining the informed consent must also sign the ICF.

Patients should be reconsented to the most current version of the ICF(s) during their participation in the study in accordance with local regulations, institutional, and IRB/IEC policy. The source document should document the reconsent process and that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

A copy of the ICF(s) must be provided to the patient.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for future research, if required by country law, regulation, and/or central/local IRB/IEC. The investigator or authorized designee will explain to each patient the objectives of the future research. Country regulations may require consent from each patient. If required, a separate consent (ie, signature) must be collected from each patient. Patients will be told that they are free

to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. Patients who decline to participate in this future research will not provide this separate signature but can still participate in this study. If separate consent is not required based on the country's regulation, then future research is not optional.

14.4. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. The Compensation Policy Document will be provided to the study site by the sponsor.

The sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as per the Compensation Policy Document.

When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

Arcus will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

At the end of the study, the investigator will receive patient data for his/her site in a readable digital format that must be kept with the study records. Acknowledgement of receipt of the data is required. Records and documents (including signed ICFs) pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion 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.

15.3. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF and keep source documents filed at the investigator's site.

Data 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.

Source documents (paper or electronic) are original documents, data, and records. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X rays, patient files, and records kept at pharmacies, laboratories, and medical technical departments involved in a clinical trial.

Study monitors will perform ongoing source document review and source data verification to confirm that data entered into the eCRF by authorized 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.

15.4. Secondary Use of Data

The sponsor maintains the right to secondary use of data in this study.

Secondary use of data describes the use of data from this study for other study/studies for purposes including, but not limited to, drug development and/or academic research. Secondary use of data also includes external offerings of study data to domestic and/or foreign organization(s), and other companies and researcher(s), on a case-by-case basis.

16. PUBLICATION POLICY

The following information is required by ICH to be in the protocol if not addressed in another document.

The results of this study may be published in peer-reviewed journals or presented at scientific meetings to openly provide information on the trial to healthcare professionals and to the public. If this is foreseen, the investigator must agree to submit all manuscripts or abstracts to the sponsor before submission or presentation. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

Authorship will be determined by the sponsor and in line with International Committee of Medical Journal Editors authorship requirements.

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18. APPENDICES

APPENDIX 1. TOXICITY MANAGEMENT GUIDELINES FOR QUEMLICLUSTAT

Toxicity management guidelines for quemliclustat are provided in Table 21 below, which is intended to provide guidance on how to manage quemliclustat (eg, continue treatment, delay treatment, resume treatment, dose reduce, permanently discontinue) for a given toxicity. For management/treatment guidelines for the signs and symptoms of toxicities listed in the table, please follow local guidelines (eg, European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], etc.) or institutional standard practice and consult the study medical monitor if there are differences between these toxicity management guidelines and local guidelines and/or institutional standard practice.

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Table 21: Toxicity Management Guidelines for Quemliclustat

Event	Severity	Quemliclustat
Infusion-related reaction (including Anaphylaxis)	Grade 1-2	• Interrupt infusion • If symptoms resolve with supportive care, consider resuming infusion. Infusion rate must be permanently reduced by 50% for Grade 2 infusion-related reactions.
	Grade 3-4 (including Anaphylaxis)	Stop infusion and permanently discontinue
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritus) For Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), see specific recommendations	Grade 1	Continue at investigator discretion
	Grade 2-3	• Consider holding • If treatment is held, consider resuming when event is Grade 1 or has improved to baseline • Consider dose reduction if recurrent
	Grade 4	Permanently discontinue
Severe cutaneous adverse reaction (SCAR) [including but not limited to Stevens Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)]	Any	Permanently discontinue
Myocarditis	Grade 2-4	• Hold for Grade 2-3. Consider resuming if a nontreatment-related cause is identified • Consider dose reduction if resuming • Permanently discontinue if Grade 4
Hepatitis/Transaminitis without elevated bilirubin	Grade 2	• Hold • Consider resuming with a one-level dose reduction when event resolves to Grade ≤ 1
	Grade 3 or 4	• Hold for Grade 3 • Resume with one-level dose reduction when event resolves to Grade ≤ 1 • Permanently discontinue for Grade 4
Hepatitis/Transaminitis with elevated bilirubin (except in Gilbert's syndrome)	Grade 1 or 2 blood bilirubin increased	• Continue at investigator discretion for Grade 1 • Hold for Grade 2 If event resolves to Grade 1, resume with a one-level dose reduction

Table 21: Toxicity Management Guidelines for Quemliclustat

Event	Severity	Quemliclustat
	Grade ≥ 3 blood bilirubin increased	Permanently discontinue
Endocrinopathies (adrenal, pituitary, diabetes)	Grade 1 or 2	Consider holding
	Grade 3 or 4	• Hold until clinical management is stable • Resume when improved to Grade ≤ 1 • Consider dose reduction if resumed
Thyroid disorder (Hypothyroidism and Hyperthyroidism)	• No discontinuation required for Hypothyroidism • For symptomatic hyperthyroidism resembling Graves-like disease, consider holding and resuming after workup is complete and there is evidence of improvement in symptoms and thyroid function tests	
Nephritis or Immune-mediated kidney injury	Grade 2	Consider holding
	Grade 3	• Hold • Consider dose reduction if resumed
	Grade 3 (recurrent) or 4	• Permanently discontinue
Diarrhea/Colitis (including Immune-mediated colitis/ Enterocolitis)	Grade 2 or 3	• Hold • Resume with one-level dose reduction when event resolves to Grade ≤ 1
	Grade 4	• Permanently discontinue
Pneumonitis (including Immune-mediated lung disease and Interstitial lung disease)	Grade 1	Monitor closely if continuing
	Grade 2	• Hold • Consider resuming when improved to Grade ≤ 1 and steroid dose is stable/decreasing at ≤ 10 mg/day (prednisone or equivalent dose) • Consider dose reduction if resuming
	Grades 3	• Hold • Resume with one-level dose reduction when event resolves to Grade ≤ 1
	Grade 3 (recurrent) or 4	• Permanently discontinue

Table 21: Toxicity Management Guidelines for Quemliclustat

Event	Severity	Quemliclustat
Pancreatitis	Grade 2	Consider holding
	Grade 3	• Hold • Resume with one-level dose reduction when event resolves to Grade ≤ 1
	Grade 3 (recurrent) or 4	• Permanently discontinue
Other (may involve any organ system)	Grade 2	• Consider dose reduction
	Grade 3	• Hold • Consider dose reduction if resumed
	Grade 3 (recurrent) or Grade 4	Permanently discontinue

APPENDIX 2. CONTRACEPTION AND BARRIER GUIDANCE

Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

- Following menarche
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to one of the following:
  1. Documented hysterectomy
  2. Documented bilateral salpingectomy
  3. Documented bilateral oophorectomy

4. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

- Postmenopausal female
  1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  2. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  3. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance for Male and Female Patients

Male Patients:

Male patients are eligible to participate if they agree to the following contraception requirement during the study intervention period and for at least 3 months after the last dose of NP-Gem and 30 days after the last dose of quemliclustat.

- Refrain from donating sperm

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant
- Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

Female Patients

Female patients are eligible to participate if they agree to use one highly effective measure of contraception during the study intervention period and for at least 6 months after the last dose of NP-Gem and minimum of 30 days after the last dose of quemliclustat.

In addition, female patients will not donate eggs for at least 6 months following discontinuation of NP-Gem treatment.

A summary of contraceptive allowed during the study is provided Table 22.

Table 22: Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)[c]
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*

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

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

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX 3. CLINICAL SAFETY LABORATORY TESTS

The laboratory tests below (Table 23) will be performed by the local laboratory. Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 6. Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations (eg, for safety concerns).

Table 23: Clinical Safety Laboratory Tests

	Parameters	
Hematology	Hematocrit Hemoglobin Platelet count Red blood cell count	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate/CO_2 Blood urea nitrogen or Urea Calcium Chloride Creatinine	Glucose (nonfasting) Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin[a] Total Protein Blood uracil[b]
Coagulation Studies	Prothrombin time/international normalized ratio (PT/INR)	Activated partial thromboplastin time (aPTT)
Serology[c]	HBcAb (Hepatitis B core antibody) HBsAg (Hepatitis B surface antigen) HBV DNA (Hepatitis B virus deoxyribonucleic acid) HCV RNA (Hepatitis C virus ribonucleic acid)	HIV-1 Ab (human immunodeficiency virus 1 antibody) HIV-2 Ab HIV viral load and CD4+ T-cell count

[a] Measure direct bilirubin if total bilirubin is above the upper limit normal (ULN).
[b] No blood uracil testing is required unless mandated by local health authority.
[c] Serology only performed at screening. No hepatitis or HIV testing is required unless mandated by local health authority or patient has a history of such infection(s).

APPENDIX 4. RECIST V1.1

Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as described below (Eisenhauer, 2009).

Measurability of Tumor at Baseline

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

- **Measurable**

  Tumor lesions: Must be accurately measured in ≥ 1 dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of:

  – 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)

  – 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)

  – 20 mm by chest X-ray

  Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)

- **Nonmeasurable**

  – All other lesions (or disease sites), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis)

  – Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques

Tumor Response Evaluation

Baseline Documentation of Target and Nontarget Lesions

- **Target lesions**

  – When > 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions

  – It may be the case that, on occasion, the largest lesion, which can be measured reproducibly, should be selected

- **Nontarget lesions**

  – All other lesions (or disease sites), including pathological lymph nodes, should be identified as nontarget lesions

– It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

Evaluation of Target Lesions

Target lesions will be evaluated and response recorded as defined in Table 24:

Table 24: Response Based on Evaluation of Target Lesions at Each Assessment

Complete response	Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to < 10 mm[a]
Partial response[b]	≥ 30% decrease in the sum of the diameters of target lesions relative to the baseline sum diameters[c]
Stable disease[b, d]	Neither a sufficient reduction to qualify as a partial response nor a sufficient increase to qualify as progression[c]
Progressive disease[b]	≥ 20% increase in the sum diameters relative to the smallest sum diameters recorded (including the baseline sum diameters) in conjunction with an increase of at least 5 mm in the smallest sum diameters or the appearance of 1 or more new lesions[c, e]

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring < 10 mm to be considered as a complete response. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of < 10 mm).
[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining partial response, stable disease, and progression.
[c] In this study, the "baseline sum diameters" is calculated based on the lesion measurements obtained at screening.
[d] Duration of stable disease is measured from the date of the first dose of investigational product (IP) until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).
[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Postbaseline, fluorodeoxyglucose positron emission tomography (FDG PET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated, and response recorded as defined in Table 25:

Table 25: Response Based on Evaluation of Nontarget Lesions at Each Assessment

Complete response	Disappearance of all nontarget lesions; all lymph nodes must be nonpathologic in size (ie, < 10 mm on the short axis)
Not complete response or not progressive disease	Persistence of one or more nontarget lesions
Progressive disease	Unequivocal progression[a] of any existing nontarget lesion or the appearance of one or more new lesions[b]

[a] The patient should stop investigational product (IP), even in the presence of a partial response or stable disease, based on assessment of target lesions.
[b] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Postbaseline, fluorodeoxyglucose positron emission tomography (FDG PET) may be useful in assessing new lesions apparent on computed tomography (CT) scan.

New Lesions

The appearance of new malignant lesions denotes progressive disease; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial response (PR) or complete response (CR). For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

Evaluation of Overall Response

Overall response based on the evaluation of target and nontarget lesions will be determined as indicated in Table 26:

Table 26: Evaluation of Overall Response at Each Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Not complete response/ nonprogressive disease	No	Partial response
Partial response	Nonprogressive disease and not evaluable[b]	No	Partial response
Stable disease	Nonprogressive disease and not evaluable[b]	No	Stable disease
Not all evaluated	Nonprogressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Noncomplete response/ nonprogressive disease	No	Noncomplete response/nonprogressive disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline.
[b] Not evaluable is defined as either when no or only a subset of lesion measured.

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