Protocol Number: CRDF-001

A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second-Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma

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Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 2 Study of Onvansertib in Combination with Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second-Line Treatment of Patients with Metastatic Pancreatic Ductal Adenocarcinoma
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1.0 Approvals

Sponsor	
Sponsor Name:	Cardiff Oncology
Representative/ Title:	[redacted]
Signature /Date:	[redacted]
ICON	
Biostatistician / Title:	[redacted]
Signature /Date:	[redacted]

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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2.0 Change History

Version/Date	Change Log
0.1/16-JUN-2021	Created as new
0.2/15-Nov-2021	Updated with Sponsor Comments
1.0/06-Dec-2021	Finalized per Sponsor Feedback
2.0/07-Mar-2025	Updates requested close to database lock
3.0/18-Mar-2025	1. MedDRA version updated to Version 24 and new section added for study periods. 2. Treatment-emergent Adverse Events (TEAE) >=10% replaced TEAEs >=5%. 3. Summaries of TEAEs leading to Interruption and modification of Onvansertib separated. 4. Missing relationship of the Adverse Events will be imputed to 'Related'. 5. "Patient" replaced with "Subject" throughout the SAP except for the protocol tile.

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3.0 Table of Contents

1.0 Approvals 1
2.0 Change History 2
3.0 Table of Contents 3
4.0 Purpose 5
5.0 Scope 5
6.0 Introduction 5
6.1 Changes from Protocol 5
7.0 Study Objectives 5
8.0 Study Design 5
8.1 Study Periods 6
8.2 Sample Size Considerations 8
8.3 Randomization 8
9.0 Study Endpoints and Analysis Sets 8
9.1 Endpoints 8
9.2 Analysis Sets 9
9.2.1 Enrolled Analysis Set 9
9.2.2 Safety Analysis Set 9
9.2.3 Evaluable Analysis Set 9
9.2.4 Pharmacodynamic Analysis Set 10
9.2.5 Pharmacokinetic Analysis Set 10
10.0 Conventions and Derivations 10
10.1 Conversion of Units 10
10.2 Body Mass Index (BMI) 10
10.3 Body Surface Area (BSA) 10
10.4 Past and Current Medical History 10
10.5 Prior and Concomitant Medications 10
10.6 Baseline Values 11
10.7 Change from Baseline 11
10.8 Derivation of Efficacy Variables 11
10.8.1 Tumor Response Endpoints 11
10.8.2 Best Overall Response 11
10.8.3 Overall Response Rate 12
10.8.4 Duration of Response 12
10.8.5 Disease Control Rate 13
10.8.6 Progression-Free Survival 13
10.8.7 Overall Survival 13
10.9 Number of Cycles 13
10.10 Cumulative Dose Planned 13
10.11 Cumulative Dose Received 14
10.12 Total Dose per Cycle 14
10.13 Dose Intensity 14
10.14 Compliance 14
10.15 Treatment Exposure 14
10.16 DLT 14
10.17 Treatment Emergent Adverse Events 14
10.18 Electrocardiogram 14
10.19 Incomplete Dates for Adverse Events and Concomitant Medications 15
10.20 Study Completion 16
10.21 Handling of Other Missing Data 16
10.22 Handling of Unscheduled Visits and Unscheduled Assessments 16
11.0 Interim Analyses 16
12.0 Statistical Methods 16
12.1 Subject Disposition 17

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12.2 Demographic and Baseline Characteristics....17
12.3 Treatments....18
12.3.1 Extent of Study Drug Exposure....18
12.3.2 Prior and Concomitant Medications/Procedures....18
12.4 Important Protocol Deviations....18
12.5 Efficacy Analyses....18
12.5.1 Hypothesis Testing Strategy....18
12.5.2 Primary Endpoint....18
12.5.3 Secondary Endpoints....19
12.5.4 Other Efficacy Analyses....19
12.6 Safety Analysis....19
12.6.1 Adverse Events....19
12.6.2 Deaths and Serious Adverse Events....21
12.6.3 DLTs....21
12.6.4 Laboratory Data....21
12.6.5 Vital Signs....22
12.6.6 Physical Examinations, ECGs, ECOG and Other Observations Related to Safety....22
12.7 Exploratory Analysis....23
12.7.1 Pharmacodynamics and Biomarkers....23
12.8 Pharmacokinetic Analyses (PK)....23
12.8.1 Pharmacokinetic Variables....23
12.8.2 Plasma Pharmacokinetic Summaries....23
13.0 References....23
14.0 Glossary of Abbreviations....24

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4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Cardiff Protocol CRDF-001 version 1.0 dated 29-Jan-2021.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol and CRF version specified in the title page. Any further changes to the protocol or CRF may necessitate updates to the SAP.

6.1 Changes from Protocol

Addition of a new study period used for the subjects who were dosed both in Safety lead-in and Treatment Period. Refer to Section 8.1.

7.0 Study Objectives

Primary Objective

- To assess the efficacy of onvansertib in combination with nanoliposomal irinotecan (nal-IRI), leucovorin and fluorouracil (5-FU) for treatment of subjects with histologically confirmed metastatic pancreatic ductal adenocarcinoma (PDAC) who have failed first line gemcitabine-based prior chemotherapy.

Secondary Objectives

- To determine the overall survival (OS) of subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin and 5-FU.
- To determine the duration of response (DOR) of subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin and 5-FU.
- To assess the frequency and severity of adverse events (AEs) in subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin and 5-FU.

Exploratory Objectives

- To identify biomarkers related to sensitivity and resistance to treatment using subject-derived organoids, blood samples, and archival tissue biopsies.
- To assess KRAS allelic burden through serial collection of circulating tumor DNA (ctDNA) and to identify blood-based biomarkers related to: (a) de novo sensitivity and (b) tumor evolution and resistance.

8.0 Study Design

This is a multicenter, open-label, single-arm study to assess the safety and preliminary efficacy of onvansertib in combination with nal-IRI, leucovorin and 5-FU as a second-line treatment in subjects with metastatic PDAC. The study will be conducted at 6 study centers in the United States.

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Subjects with PDAC must have histologically confirmed measurable and metastatic disease for study eligibility. In addition, subjects must have failed treatment with one line of gemcitabine-based prior chemotherapy.

This study will consist of a Screening Period, a Safety Lead-in, a Treatment Period (Phase 2) conducted in 14-day cycles, End-of-Study (EOS) evaluations, and a Follow-Up Period.

Within 28 days prior to the first onvansertib (study drug) dose, Screening assessments will be performed.

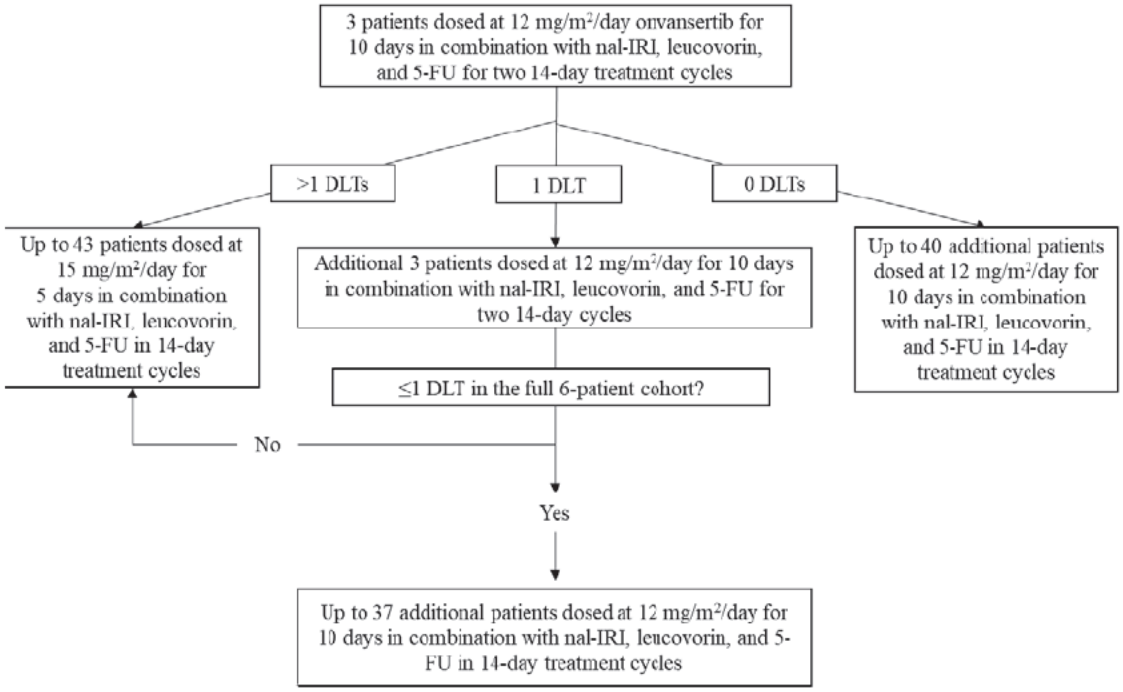
The purpose of the Safety Lead-in is to assess the safety and tolerability of a modified onvansertib dose, and dosing schedule of 12 mg/m^2 QD for 10 days (Day 1 to Day 10) of a 14-day treatment cycle. The safety and tolerability of onvansertib 15 mg/m^2 QD for 5 days (Day 1 to Day 5) of a 14-day treatment cycle in combination with FOLFIRI (5-fluourouracil, leucovorin, irinotecan) and bevacizumab has been previously established. The recommended dose and regimen (either 12 mg/m^2 QD for 10 days in a 14-day treatment cycle or 15 mg/m^2 QD for 5 days in a 14-day treatment cycle) in combination with nal-IRI, leucovorin and 5-FU for the study will be determined in the Safety Lead-in based on the overall safety profile of each dose and dosing regimen, including dose-limiting toxicities (DLTs), drug modifications and reductions, and AEs.

8.1 Study Periods

DLT evaluation: The DLT evaluation period is the first two 14-day cycles of treatment (28 days in total) plus an additional 2 weeks for any hematologic DLTs to resolve Grade 2 or less or any nonhematologic DLT to resolve to Grade 1 or less. Any Grade ≥ 3 adverse events, irrespective of drug attribution, is considered a **DLT**. At the end of the DLT evaluation period, safety data for the initial 3 subjects will be reviewed by the Investigators and the sponsor for evaluation of DLTs or other safety events determined by the Investigators and Sponsor to be unacceptable. Depending on the results, the Safety Lead-in cohort may be expanded, or dosing of all subsequent subjects in the trial will commence (see Figure 1).

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Figure 1 Safety Lead-in Flow Chart



5-FU=fluorouracil; DLT=dose-limiting toxicity; nal-IRI=nanoliposomal irinotecan

Safety Lead-in: The Safety Lead-in period involves administering Onvansertib at a dose of 12 mg/m² orally (PO) from Day 1 to Day 10 of each 14-day cycle. This will be given in combination with nal-IRI 70 mg/m² (50 mg/m² for subjects homozygous for UGT1A1*28), leucovorin 400 mg/m², and 5-FU 2400 mg/m², all administered sequentially on Day 1 of each 14-day cycle.

Treatment Period: For Phase 2, the Treatment Period will commence with the onvansertib dose selected based on the results of the Safety Lead-in. Radiographic disease assessment by CT or MRI using RECIST v1.1 will be performed at screening, then every 8 weeks after starting treatment (prior to Day 1 of Cycle 5 and every 4th cycle thereafter, i.e., prior to Day 1 of Cycles 9, 13, 17, 21, etc.), and at EOS. Subjects will continue treatment in this study (Cycle 1, Cycle 2, Cycle 3, etc.) until disease progression (PD) or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Prior to the start of each treatment cycle, subjects will have blood samples drawn for hematology. Only subjects with absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L and platelets ≥ 100 × 10^9/L will continue with study treatment for that cycle; subjects not meeting this threshold will resume treatment when these criteria are met. Other non-hematological lab parameters should be within range per eligibility criteria mentioned in Protocol.

Safety Lead-in to Treatment Period: This study period is added on sponsor's request for the summary tables as some of the subjects who were in Safety Lead-in (12 mg/m2) transitioned to the Treatment Period to take 15 mg/m2. For the purposes of analysis, these subjects will be counted to be in the treatment period in a separate column and will not be included in the Safety Lead-in or the Treatment Period column counts. Although for efficacy analysis, total counts for the Treatment Period will be the sum of the subjects in the Safety Lead-in to Treatment Period and Treatment Period into a new column called "Treatment Period Total".

The EOS visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered.

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8.2 Sample Size Considerations

The total planned sample size is at least 46 subjects, if 43 subjects are enrolled at 15 mg/m^2/day onvansertib after 3 subjects are dosed at 12 mg/m^2/day onvansertib. The primary efficacy endpoint is the overall response rate (ORR) by RECIST v1.1.

The primary endpoint will be tested in a Fleming single-stage design. The null hypothesis for ORR that the true ORR is 7.7% will be tested against a one-sided alternative of 20% ORR.

The null hypothesis on ORR will be rejected if 6 or more responses are observed in the first 39 evaluable subjects. Evaluable subjects are defined as those who complete at least 2 cycles of onvansertib in combination with nal-IRI, leucovorin and 5-FU. For the primary endpoint, the sample size will provide 80% power to reject the alternative hypothesis with type I error rate of 0.1 (actual error rate of 0.076; PASS 14 Power Analysis and Sample Size Software v14.0.05). Four additional subjects will be enrolled to consider ineligibility, withdrawals, etc.

8.3 Randomization

Not applicable as this is a single-arm study.

9.0 Study Endpoints and Analysis Sets

9.1 Endpoints

Objectives	Endpoint
Primary	Primary endpoint
• To assess the efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5 FU for treatment of subjects with histologically confirmed metastatic PDAC who have failed first line gemcitabine-based prior chemotherapy.	• Overall response rate (ORR) by RECIST v1.1.
Secondary	Secondary endpoint
• To assess the frequency and severity of adverse events (AEs) in subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5 FU	• Treatment safety based on toxicities evaluated according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 in subjects who have received at least one dose of onvansertib
• To determine the OS of subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5 FU	• Median overall survival (OS)
• To determine the DOR of subjects with metastatic PDAC treated with onvansertib in combination with nal-IRI, leucovorin, and 5 FU	• Duration of response (DOR)

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• Further to assess the efficacy of onvansertib in combination with nal-IRI, leucovorin, and 5 FU for treatment of subjects with histologically confirmed metastatic PDAC	• ORR in subjects who complete 2 cycles of onvansertib, in combination with nal-IRI, leucovorin, and 5 FU • Disease control rate (DCR; defined as CR, PR or SD) by RECIST v1.1 over the entire Treatment Period of Phase 2 • Reduction (≥50% from baseline) in serum CA 19-9 response
Exploratory	Exploratory endpoint
• To identify biomarkers related to sensitivity and resistance to treatment using subject-derived organoids, blood samples, and archival tissue biopsies	• Establishment of subject-derived organoids from tissue biopsies to perform pharmacosensitivity, genomic and transcriptomic analyses, and identify biomarkers associated with treatment response • Genomic profiling of ctDNA at baseline and PD to identify genomic markers associated with subject sensitivity and resistance to treatment • Use of archived tumor tissue biopsy samples (if available) to evaluate genomic profiles (DNA/RNA) associated with subject response
• To assess KRAS allelic burden through serial collection of circulating tumor DNA (ctDNA) and to identify blood based biomarkers related to: (a) de novo sensitivity and (b) tumor evolution and resistance	• Assessment of KRAS allelic burden in liquid biopsies as measured by ctDNA

9.2 Analysis Sets

9.2.1 Enrolled Analysis Set

The Enrolled Analysis Set includes all subjects who were enrolled in the study, i.e., completed the informed consent and did not fail screening. This analysis set will be used to summarize subject analysis sets and subject disposition.

9.2.2 Safety Analysis Set

The Safety Analysis Set includes all subjects who have received at least one dose (even partially) of any study drug, i.e., onvansertib, nal-IRI, leucovorin or 5-FU. This analysis set will be used for safety analysis.

9.2.3 Evaluable Analysis Set

The Evaluable Analysis Set includes subjects who have taken at least 1 dose of Onvansertib in the first 2 cycles. This analysis set will be used for efficacy analysis.

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9.2.4 Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set includes subjects who have at least 1 evaluable paired pharmacodynamic measures of pre- and post-administration of the study treatment onvansertib, in combination with nal-IRI, leucovorin and 5-FU. This analysis set will be used for analysis of pharmacodynamics, tumor biomarkers and genomic profiles. This is out of scope of this analysis plan.

9.2.5 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes subjects who have completed protocol-specified onvansertib dosing in cycle 1 and have sufficient PK assessments to permit estimation of PK concentrations. This analysis will be used to summarize PK evaluations.

10.0 Conventions and Derivations

10.1 Conversion of Units

- 1 week = 7 days, 1 Month = 30.4375 days, 1 year = 365.25 days.
- Height in Meters = (Height in Centimeters) / 100, rounded to 1 decimal place.
- Weight in Kilograms = Weight in Pounds / 2.2, rounded to 1 decimal place.
- Height in Centimeters = Height in Inches * 2.54, rounded to 1 decimal place.
- Temperature in °Celsius = (Temperature in °Fahrenheit - 32) x 5) / 9, rounded to 1 decimal place.

10.2 Body Mass Index (BMI)

BMI = Weight (kg)/ height $(m)^2$

If either height or weight are missing, then BMI will not be calculated.

10.3 Body Surface Area (BSA)

BSA will be calculated using the DuBois formula:

BSA (m^2) = 0.007184 x screening height $(cm)^{0.725}$ x weight $(kg)^{0.425}$

If either height or weight are missing, then BSA will not be calculated.

10.4 Past and Current Medical History

Past medical histories are those with a stop date prior to the first dose of any study drugs.

Current medical histories are those that started prior to enrollment in the trial but are ongoing on or after the first administration of study drugs.

10.5 Prior and Concomitant Medications

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the subject at any time during the study starting at the time that the first dose of study drugs was administered through the final study visit assessment.

Prior treatments are defined as those with a stop date prior to the first dose of study treatment and taken within 28 days prior to enrollment.

Concomitant medications refer to those medications that were initiated either before or after the first dose of the study treatment and are either ongoing at the start of the study or discontinued after the treatment has begun.

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10.6 Baseline Values

Unless otherwise specified, Baseline will be defined as the most recent non-missing value prior to the first dose of the study treatment. If an assessment qualifying as baseline occurs on the same date as the treatment but the time is not recorded, it will still be considered prior to the first dose and will qualify as the baseline.

10.7 Change from Baseline

The change from baseline value is defined as the value at any given post-baseline point minus the baseline value.

10.8 Derivation of Efficacy Variables

10.8.1 Tumor Response Endpoints

At each tumor response assessment, all treatment decisions based on radiographic scans will be at the discretion of the treating investigator. The overall response will be assessed based on RECIST 1.1 [(1)] assessment criteria.

Tumor responses will be assessed by the Investigator until the end of treatment.

RECIST v1.1 has the following possible overall response categories (ordered from the best response to worst): Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD). In case the overall response is not evaluable, it'll be categorized under "Not Evaluable (NE)" at the end

10.8.2 Best Overall Response

Per RECIST (v 1.1): Best overall response (BOR) will be programmatically derived based on reported timepoint response assessments at different evaluation timepoints from the first dose date until the first documented disease progression, death.

A Best Response of CR or PR, as shown Table 1 below, cannot be assessed unless it is confirmed at the subsequent assessment (at least 28 days between assessments after the first post baseline disease assessment).

Subjects with inadequate data for tumor assessment (e.g., no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of response rate.

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Table 1 Confirmed Response based on Subsequent Assessments

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Response) *
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	ND (remains on treatment)	uCR
PR	CR	PR
PR	PR	PR
PR	SD (3) *	SD
PR	NE **	SD or NE (2)
PR	ND (remains on treatment)	uPR
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

Abbreviations: PD=Progressive Disease; NE= Not Evaluable; CR=Complete Response; PR=Partial Response; ND=Not Done; SD=Stable Disease; uCR=unconfirmed Complete Response; uPR=unconfirmed Partial Response.

* A Best Response of SD can only be made after the subject is on-study for a minimum of 8 weeks. If the subject is on-study less than 8 weeks (-7 days) i.e. 49 days, any tumor assessment indicating stable disease before this time will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third Time Point Response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR).

(1) Best response will be SD if the first TPR is after at least 8 weeks on-treatment. Otherwise, the best response will be PD.

(2) Best response will be SD if the first TPR is after 8 weeks on-study. Otherwise, the best response will be NE.

(3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.

10.8.3 Overall Response Rate

Overall Response Rate (ORR) is defined as the percentage of subjects who achieved the best overall response of confirmed Complete Response (CR) or Partial Response (PR) determined by the Investigator per RECIST v1.1[(1)].

10.8.4 Duration of Response

Duration of Response (DOR) in subjects who experience confirmed CR or PR will be assessed from the date of first response to the date of their last evaluable response assessment or the first date of recurrence or progression of disease, or date of all-cause death, whichever occurs first.

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DOR will be calculated as the time in months from assessment date of first confirmed response (CR or PR) until documentation of recurrence or progression of disease, or all-cause death:

DOR = (date of documentation of recurrence or progression of disease or all-cause death – assessment date of first confirmed CR or PR + 1) / 30.4375

DOR will only be calculated for the subgroup of subjects achieving a confirmed CR or PR.

Event times will be censored at the date of the last evaluable assessment confirming CR or PR response for subjects on-study and progression-free. If the date of the last evaluable assessment is unavailable data will be systematically censored at the time of analysis.

10.8.5 Disease Control Rate

Disease Control Rate (DCR) is defined as the percentage of subjects who achieved the best overall response of confirmed CR or PR, or Stable Disease (SD) determined by the Investigator per RECIST v1.1, over the entire Treatment Period.

10.8.6 Progression-Free Survival

Progression-Free Survival (PFS), in months, is defined as from first administration of study treatments until first observation of disease progression that is subsequently confirmed, or death due to any cause, whichever occurs first.

PFS = (Date of first progression or death – date of first dose of study treatment + 1) / 30.4375

The date of response or progression will be the date of assessment recorded for the tumor evaluation for each applicable timepoint.

Event times will be censored on the date of the last evaluable assessment documenting response and progression-free. If the date of the last evaluable assessment is unavailable data will be systematically censored at the time of analysis.

10.8.7 Overall Survival

Overall Survival (OS), in months, is defined as the time from the first dose of study treatments to death of any reason:

OS = (date of death – date of first dose of study treatments + 1) / 30.4375.

For the subjects who do not have documented death, the event time will be censored at the date of last evaluable assessment or date last known to be alive. If the last evaluable assessment date is unavailable, the date of analysis will be used systematically.

10.9 Number of Cycles

The number of cycles is defined as the total number of treatment cycles initiated with Onvansertib or standard of care.

10.10 Cumulative Dose Planned

Cumulative dose planned is defined as the sum of the total dose in all the planned cycles. Within each cycle, the total number of days the subject is scheduled to dose is multiplied by the one-day dose calculation as below:

1. Multiply the assigned dose (12 or 15 mg) and the BSA.
2. Round the one-day dose value to the nearest whole number.
    a. If the rounded one-day dose is <=23 then assign the value 20.
    b. If the rounded one-day dose is >=24 and <=27 then assign the value 25.

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c. If the rounded one-day dose is >=28 and <=32 then assign the value 30.

d. If the rounded one-day dose is >32 then assign the value 35.

10.11 Cumulative Dose Received

Cumulative dose received is defined as the sum of Total dose (mg) as recorded on the Onvansertib and Standard of Care treatment CRFs.

10.12 Total Dose per Cycle

Total dose per cycle is calculated per subject as the average of the Total Dose taken in all the cycles.

10.13 Dose Intensity

Relative Dose Intensity (%) will be calculated as:

- Relative Dose Intensity (%) = (cumulative dose received in mg / cumulative dose planned in mg) * 100

10.14 Compliance

Compliance is calculated as:

- Compliance (%) = (number of doses received / number of doses expected) * 100

For Onvansertib, the number of planned doses is calculated by multiplying the number of treatment cycles by 10 during the Safety Lead-in period or by 5 during the Treatment Period, depending on the selected regimen. For other drugs, the number of planned doses corresponds to the number of treatment cycles. If a subject transitions from the Safety Lead-in to the Treatment Period, the planned dose will be calculated per the Treatment Period and will be multiplied by 5.

10.15 Treatment Exposure

Duration of Exposure (weeks) will be calculated as:

Duration of Exposure (weeks) = (date of last non-zero dose of study treatment – date of first dose of study treatment + 1) / 7.

Duration of Exposure for each subject will be calculated separately for each study drug.

10.16 DLT

A DLT is defined as any grade ≥ 3 AE (recorded on the CRF) according to NCI-CTCAE version 5.0, irrespective of drug attribution. The DLT evaluation period for subjects in the Safety Lead-in is the initial two 14-day cycles, plus an additional 2 weeks for a hematologic DLT to resolve to Grade 2 or less, or a nonhematologic DLT to resolve to Grade 1 or less, if warranted.

10.17 Treatment Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs that first occurred or worsened in severity on or after the first administration of study treatments and up to 30 days after the last administration of study treatments.

10.18 Electrocardiogram

Twelve-Lead electrocardiograms (ECGs) will periodically be performed in triplicate and the following information from the CRF for analysis:

- mean heart rate (beats/min)
- mean P-R interval (msec)

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- mean QRS interval (msec)
- mean QT interval (msec)
- mean R-R interval (msec)
- mean QTc (msec) by the Fridericia's formula, QTcF
- indicator of clinically significant ECG

10.19 Incomplete Dates for Adverse Events and Concomitant Medications

For analysis of AEs and concomitant medications, a complete date must be established to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or medications will be displayed as reported in the subject data listings (i.e. no imputed values will be displayed in data listings).

Start Date

If the start date is completely missing (i.e., the day, month, and year are all unknown), the start date will be set to the date of first dose of study treatment, except that no imputation will be performed for medications with completely missing start dates.

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if years are the same, but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same, but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as also missing and both month and day will be replaced according to the procedure below.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the **first dose date**, then January 1 will be assigned to the missing fields.
- If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Stop Date

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same, but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.

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- If either the year is after the year of the **last visit date** or if both years are the same, but the month is after the month of the **last visit date**, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the procedure below.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then December 31 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then Jan 1 will be assigned to the missing fields.

10.20 Study Completion

Study Completion is defined as completing the EOT visit and remaining in follow-up for survival and disease progression for 1-year post-EOT.

10.21 Handling of Other Missing Data

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings as available in the database.

10.22 Handling of Unscheduled Visits and Unscheduled Assessments

Unscheduled assessments will only be included in deriving the maximum post baseline grade for the lab, ECG shift tables and End of study ECOG score.

11.0 Interim Analyses

There is no interim analysis planned.

12.0 Statistical Methods

The primary analysis will be performed when the last subject has completed the EOS Visit.

All analyses and generation of tables, figures, subject data listings, and statistical output will be performed using SAS version 9.4 or higher. Standard summary statistics for continuous and discrete variables will be presented. Unless otherwise noted, categorical variables will be summarized using counts and percentages. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Percentages will be rounded to one decimal place, except that 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (STD), median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, median, Q1, and Q3 to an additional decimal place and the STD to two additional decimal places.

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All data will be summarized separately for the treatment periods (see Section 8.1), **Safety Lead-in**, **Safety Lead-in to Treatment Period and Treatment Period**. All subjects presented will be mutually exclusive as subjects transitioning from Safety Lead-in to Treatment period will not be repeated in Safety Lead-in and/or Treatment Period columns. Efficacy analysis will also present combined results of the Safety Lead-in to Treatment Period and Treatment Period in addition to the three summaries.

For the summaries involving visits, only scheduled visits will be presented unless otherwise specified.

12.1 Subject Disposition

The number and percentage of subjects who completed study and who discontinued study along with the reason for discontinuation will be tabulated.

See definition of Study Completion in Section 10.20.

The number of subjects in each analysis set will also be presented for all enrolled subjects.

A tabulation of the number and percentage of subjects enrolled at each center will be presented.

All subject disposition data will be listed.

12.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects on the Safety Analysis Set. Gender, race, and ethnicity will be presented using number and percentage of subjects. weight, height, BMI and BSA will be summarized using the number of subjects, mean, Standard Deviation (STD), minimum and maximum.

The number and percentage of subjects with a medical/surgical history condition will be summarized overall and by MedDRA® (version 24) system organ class (SOC) and preferred term (PT) for the Safety Analysis Set.

Baseline disease characteristics such as tumor type, Grade at Initial Diagnosis, Tumor Stage at Initial Diagnosis, disease stage at study entry and cancer duration in years: (screening date - date of initial diagnosis + 1) / 365.2425, will be tabulated for the Safety Analysis Set.

Prior radiation therapy variables will be presented for the most recent regimen in the Safety Analysis Set. The variables to be considered are:

- Therapy type
- Intent
- Setting
- Modality type
- Best overall response

Prior systemic anticancer therapy will be presented for the most recent therapy in the Safety Analysis Set. The variables to be considered are:

- Type of therapy
- Time of most recent therapy in years: (screening date - date of most recent therapy) / 365.2425
- Best response
- Reason for stopping therapy

The demographics, baseline disease characteristics, medical history, cancer history and prior radiotherapy data will be listed.

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12.3 Treatments

12.3.1 Extent of Study Drug Exposure

Descriptive statistics for each study drug will be provided for the duration of exposure (weeks), cumulative dose per subject, relative dose intensity, number of treatment cycles and compliance.

The number and percentage of subjects with at least 1 dose modification/interruption and reason for Change/Interruption will be presented for onvansertib.

The number and percentage of subjects with at least 1 dose interruption and reasons for interruptions, subjects with at least 1 dose modification and reasons for modification and Duration of interruption will be presented for Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil.

All drug administration and compliance data will be listed.

12.3.2 Prior and Concomitant Medications/Procedures

Prior and Concomitant medications are categorized by Preferred Term (PT) per the WHO Drug Dictionary (March 2021) and will be summarized by the Safety Analysis Set. Primary Indication for the use of the medication will also be summarized as recorded in the CRF.

The number and percentage of subjects with concomitant procedures will be summarized by the reported procedures for the Safety Analysis Set. Procedures used on whether to treat AE or not will also be summarized as recorded in the CRF.

All prior, concomitant medications and procedures will be listed.

12.4 Important Protocol Deviations

Per ICON processes, important protocol deviations data will be entered into our system of record (PSO). The study team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as it seems appropriate.

Based on the protocol deviations data entered the Clinical Trial Management System (CTMS), the important protocol deviations will be tabulated using incidence by deviation type on the Safety Analysis Set. All protocol deviations will be listed by the Enrolled Analysis Set.

12.5 Efficacy Analyses

All efficacy analyses will be based on the Evaluable Analysis Set unless otherwise mentioned. No imputation methods will be applied to the primary and secondary endpoints of the trial. All available data will be summarized as appropriate.

12.5.1 Hypothesis Testing Strategy

No formal hypothesis testing will be done. Hypothesis testing is for study design purposes and not for inferential purposes.

12.5.2 Primary Endpoint

12.5.2.1 Overall Response Rate (ORR)

The number and percentage of subjects having the best overall response for each response (CR, PR, SD, PD and NE) will be provided. The number and percentage of subjects with ORR will be provided. Also, the Clopper-Pearson 2-sided 95% confidence interval (CI)[2] associated with ORR will be presented.

The waterfall plot for the best overall response will be presented. Swimmer plot for the best overall response and spider plot for sum of tumor measurements over time will also be presented.

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12.5.3 Secondary Endpoints

12.5.3.1 Duration of Response

The number and percentage of subjects with confirmed responses and censored subjects will be presented. The 25th percentile, 50th percentile (median), and 75th percentile DOR and corresponding 95% CIs will be estimated using the Kaplan-Meier method. A Kaplan-Meier plot of DOR will be presented. The count and percentage of responding subjects who have an event or are censored will be summarized.

This will only be done for the subset of subjects who have had a response (CR or PR).

12.5.3.2 Progression-Free Survival

The number and percentage of responding subjects who have an event or are censored will be summarized. The 25th, 50th (median) and 75th percentile and corresponding 95% CIs estimated using the Kaplan-Meier method will be presented. A Kaplan-Meier plot of PFS will be presented.

PFS data listing will also be provided.

12.5.3.3 Overall Survival

The number and percentage of subjects who have an event or are censored will be summarized. The 25th, 50th (median) and 75th percentile and corresponding 95% CIs estimated using the Kaplan-Meier method will be presented. A Kaplan-Meier plot of OS will be presented.

OS data listing will also be provided.

12.5.4 Other Efficacy Analyses

12.5.4.1 Disease Control Rate (DCR)

The number and percentage of subjects with DCR will be provided. Also, the Clopper-Pearson 2-sided 95% CIs associated with DCR will be presented.

All efficacy data will be provided in the data listing.

12.6 Safety Analysis

All safety analyses will be performed on the Safety Analysis Set.

12.6.1 Adverse Events

Adverse events will be tabulated by the following categories:

- Any adverse events
- Treatment-emergent adverse events
- Treatment-related (onvansertib) treatment-emergent adverse events
- Treatment-related (nal-IRI) treatment-emergent adverse events
- Treatment-related (leucovorin) treatment-emergent adverse events
- Treatment-related (5-FU) treatment-emergent adverse events
- Grade 3 or greater treatment-emergent adverse events
- Grade 3 or greater treatment-related (onvansertib) treatment-emergent adverse events
- Grade 3 or greater treatment-related (nal-IRI) treatment-emergent adverse events
- Grade 3 or greater treatment-related (leucovorin) treatment-emergent adverse events
- Grade 3 or greater treatment-related (5-FU) treatment-emergent adverse events

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- Serious treatment-emergent adverse events
- Treatment-related (onvansertib) serious treatment-emergent adverse events
- Treatment-related (nal-IRI) serious treatment-emergent adverse events
- Treatment-related (leucovorin) serious treatment-emergent adverse events
- Treatment-related (5-FU) serious treatment-emergent adverse events
- Treatment-emergent adverse events leading to discontinuation of onvansertib
- Treatment-emergent adverse events leading to dose modification of onvansertib
- Treatment-emergent adverse events leading to interruption of onvansertib
- Treatment-emergent adverse events leading to discontinuation of nal-IRI
- Treatment-emergent adverse events leading to dose interruption of nal-IRI
- Treatment-emergent adverse events leading to dose modification of nal-IRI
- Treatment-emergent adverse events leading to discontinuation of leucovorin
- Treatment-emergent adverse events leading to dose interruption of leucovorin
- Treatment-emergent adverse events leading to dose modification of leucovorin
- Treatment-emergent adverse events leading to discontinuation of 5-FU
- Treatment-emergent adverse events leading to dose interruption of 5-FU
- Treatment-emergent adverse events leading to dose modification of 5-FU
- Treatment-related (onvansertib) treatment-emergent adverse events leading to discontinuation of onvansertib
- Treatment-related (nal-IRI) treatment-emergent adverse events leading to discontinuation of nal-IRI
- Treatment-related (leucovorin) treatment-emergent adverse events leading to discontinuation of leucovorin
- Treatment-related (5-FU) treatment-emergent adverse events leading to discontinuation of 5-FU
- Treatment-emergent adverse events resulting in death
- Treatment-emergent adverse event by relationship to onvansertib
- Treatment-emergent adverse events experienced by >= 10% of subjects
- Any observed DLTs

For the overall table, the number of subjects is counted only once within each AE category, and percentages are calculated based on the safety population.

The number of events included in any of the summaries refers to the total number of AEs within the category of AE, SOC or PT.

A breakdown of the number and percentage of subjects reporting each adverse events listed above, categorized by SOC and preferred term coded according to the MedDRA dictionary, and by the CTCAE Grade (v5) will be presented. Subjects are counted once within each SOC or preferred term.

Tabulation of data, categorized by relationship to onvansertib as Unrelated (Unrelated, Unlikely) and Related (Possibly, Probably and Definitely related) as recorded on the CRF, will be presented. AEs with missing relationship to the treatment will be imputed as 'Related' (to that treatment) in the summaries. For

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each SOC or preferred term, subjects are counted only once within relationship, in their worst CTCAE grade even if they experienced multiple events in that category.

A summary of reported events, categorized by NCI CTCAE Grade (Version 5.0) (Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life threatening], Grade 5 [fatal]), will also be provided. Subjects with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event within that SOC or preferred term.

A further tabulation presenting commonly occurring TEAEs, defined as those that occur in 10% or more of subjects by SOC and preferred term will be will also be presented.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

12.6.2 Deaths and Serious Adverse Events

Subject death will be listed by subject by presenting date of death, primary reason for death. Adverse events as reason for death will also be listed. A separate by subject table will detail the deaths with the Adverse events details and relatedness to the treatments.

Serious adverse events will be tabulated by SOC and PT, as well as by relationship to study drug. These will also be presented in a separate by subject table which will detail the serious TEAEs along with relatedness to the treatments. The listing of all treatment-emergent adverse events by subject will also highlight the reasons for seriousness in case the AE is serious.

12.6.3 DLTs

The incidence of DLTs occurring in study will be tabulated by SOC and PT.

12.6.4 Laboratory Data

The following laboratory assessments and parameters will be summarized in this trial. The units in which each of this laboratory parameters will be summarized is presented in Table 12.6-1.

Table 12.6-1 Laboratory Assessments

Laboratory Assessment	Parameter	Standard Unit
Hematology	Basophils	x10^9/L
	Basophils/Leukocytes	fraction of 1
	Eosinophils	x10^9/L
	Eosinophils/Leukocytes	fraction of 1
	Hematocrit	fraction of 1
	Hemoglobin	g/L
	Lymphocytes	x10^9/L
	Lymphocytes/Leukocytes	fraction of 1
	Monocytes	x10^9/L
	Monocytes/Leukocytes	fraction of 1
	Neutrophils	x10^9/L
	Neutrophils/Leukocytes	fraction of 1
	Platelets	x10^9/L
	RBC	x10^12/L
	WBC	x10^9/L
Clinical Chemistry	Albumin	g/L
	Alkaline Phosphatase	ukat/L

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	Alanine Aminotransferase	ukat/L
	Aspartate Aminotransferase	ukat/L
	Bicarbonate	mmol/L
	Calcium	mmol/L
	Chloride	mmol/L
	Creatinine	umol/L
	Bilirubin Total	umol/L
	Glucose	mmol/L
	Phosphate	mmol/L
	Magnesium	mmol/L
	Potassium	mmol/L
	Sodium	mmol/L
	Urea Nitrogen	mmol/L

A descriptive summary (n, mean, STD, median, Q1, Q3, minimum, and maximum) of absolute value and change from baseline value for hematology, clinical chemistry will be provided.

Shift tables for some hematology and chemistry will be provided for the maximum post-baseline grade including data from any scheduled and unscheduled visits prior to or on end of treatment visit. These tables will compare the NCI-CTCAE v5.0 grade (0 to 4) for the baseline value relative to the worst post-baseline CTCAE grade for all non-missing post-baseline data. The NCI-CTCAE Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Subjects meeting shift criteria for high values as well as low values during the trial will be summarized for both criteria. Lowest of the possible grades will be assigned if the grade categories are only distinguished by the clinical signs or symptoms.

The hematology and clinical chemistry data will all be listed.

12.6.5 Vital Signs

Vital signs measurements will include Diastolic and Systolic blood pressure (mmHg), Heart rate (beats/minute), Respiratory rate (breaths/min), Temperature (°C), Height (cm), weight (kg) and BSA (m^2).

A descriptive summary (n, mean, STD, median, Q1, Q3, minimum, and maximum) of absolute value and change from baseline value for vital signs will be provided.

A summary of abnormal vital signs by time point will be presented, where abnormal vital signs are systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, heart rate <60 beats/min or >100 beats/min, respiratory rate >20 breaths/min or <12 breaths/min and Temperature ≥ 38°C or < 36.1°C.

12.6.6 Physical Examinations, ECGs, ECOG and Other Observations Related to Safety

Twelve-lead electrocardiograms (ECGs) will be performed in triplicate and the average of all numeric readings at a specified visit will be used. Baseline will be defined as the average of all pre-dose ECG readings for tables presenting change from Baseline of all numerical parameters: QTcF (msec), QT (msec), PR Interval (msec), RR Interval (msec) and QRS Duration (msec). For the non-numeric assessments, the baseline would be the last collected assessment among the triplicate assessments. For all post-Baseline visits, the average of all interpretable readings at the specified visit will be used for summaries.

A descriptive summary (n, mean, STD, median, Q1, Q3, minimum, and maximum) of absolute value and change from baseline value for ECG parameters will be provided. Tables will also present the Baseline NCI CTCAE Grade and the shift to the Maximum NCI CTCAE Grade post-baseline for QTcF. The number and percentage of subjects with abnormal QTcF values (based on the average of the triplicate results) at the

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maximum post-baseline QTcF and the change from baseline QTcF will be summarized according to the ICH E14 Category below:

Absolute Values
- ≤ 450 msec
- > 450 msec to ≤ 480 msec
- > 480 msec to ≤ 500 msec
- > 500 msec

Change from Baseline
- ≤ 30 msec
- > 30 msec to ≤ 60 msec
- > 60 msec

ECG data will be presented in a subject data listing.

The subject data listings will be provided for other safety parameters: Physical Examination, Pregnancy Test Results, and ECOG Performance Status.

12.7 Exploratory Analysis

12.7.1 Pharmacodynamics and Biomarkers

Pharmacodynamic biomarkers analyses are out of scope of this SAP and will only be listed.

12.8 Pharmacokinetic Analyses (PK)

12.8.1 Pharmacokinetic Variables

Concentrations of Onvansertib (and other analytes) will be collected in plasma.

12.8.2 Plasma Pharmacokinetic Summaries

12.8.2.1 Plasma Concentrations

Plasma concentrations of Onvansertib (and other analytes) collection in ng/mL with Lower limit of quantification (LLOQ) below a certain value will be set to missing for the analysis value and will be excluded from the computation of mean concentration and natural log transformation values.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation (STD), coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations at each scheduled time point.

Linear and Semi-logarithmic (±STD) plots of the arithmetic mean plasma concentration by scheduled sampling time will also be provided by study period. These plots will show time in hours.

All individual subject plasma concentration data will be listed by subject and dose.

13.0 References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.
2. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-13.

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
BSA	Body Surface Area
CRF	Case Report Form
CSR	Clinical Study Report
CR	Complete Response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End-of-Study
5-FU	fluorouracil
MRI	Magnetic resonance imaging
nal-IRI	Nanoliposomal irinotecan
NE	Not Evaluable
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	Orally
PR	Partial response
QD	Once daily
Q1	25th percentile
Q3	75th percentile

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RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable disease
STD	Standard Deviation
TEAE	Treatment Emergent Adverse Event

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