Protocol Number: TROV-054

Official Title: A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with FOLFIRI and Bevacizumab for Second-Line Treatment of Metastatic Colorectal Cancer in Patients with a KRAS Mutation

NCT Number: NCT03829410

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16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

Final SAP, Version 1.1, dated 25 Mar 2024

16.1.9.2 Supportive SAS Outputs (Available on Request From the Sponsor)

Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with FOLFIRI and Bevacizumab for Second-Line Treatment of Metastatic Colorectal Cancer in Patients with a KRAS Mutation
Protocol Version No./Date:	1.4 and 2.0/17-Dec-2019 and 26-Oct-2021
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1.0 Approvals

Sponsor	
Sponsor Name:	Cardiff Oncology, Inc.
Representative/ Title:	[redacted]
Signature /Date:	[redacted]
[redacted]	
Biostatistician / Title:	[redacted]
Signature /Date:	[redacted]

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

2.0 Change History

Version/Date	Change Log
0.1	Created per Protocol v2.0, while incorporating comments for previous drafts per Protocol v1.0.
0.2	Refer section 6.1 for details. Updated per sponsor comments and additional updates to the efficacy analysis.
1.0	Addition of KRAS mutation Allelic burden outputs and figures
1.1	Analysis Sets definition update

3.0 Table of Contents

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 Oncology, Inc. Protocol TROV-054.

5.0 Scope

The Statistical Analysis Plan outlines the following:

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

See Glossary of Abbreviations for a list of abbreviations used throughout this document. The list of the mock tables, figures, and listings (TFLs) depicting the analyses described in this SAP are presented in a separate document.

6.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Cardiff Oncology, Inc. Protocol TROV-054.

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 versions specified in the title page. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of the first draft of the SAP will be tracked in the SAP Change Log; the final version of the SAP will be issued for sponsor approval prior to database lock. Any deviations from the final version of the SAP will be documented in the final Clinical Study Report (CSR).

6.1 Changes from Protocol

Following were the key reasons for Protocol Amendment v2.0 from v1.0:

- The completion of Phase 1b, with the determination of the recommended phase 2 dose (RP2D) and maximum tolerated dose (MTD) of 15 mg/m^2, which are identical.
- Sample size for Phase 2 increased from 26 to approximately 80 patients.
- Primary, secondary, and exploratory statistical endpoints and analyses were revised. Safety analyses revised.
- Inclusion and Exclusion Criteria were revised.
- Confirmation by liquid biopsy of Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation status is not required for study eligibility. Already established requirement for documentation of KRAS mutation in exon 2, 3, or 4 in primary tumor or metastasis, assessed by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, is still required.
- Patients must have formalin-fixed, paraffin-embedded (FFPE) tumor tissue (newly acquired or archival) for study eligibility.
- PK sampling times revised and new food effect substudy added with sampling times.
- Revised schedule for collection of circulating tumor DNA (ctDNA) and deleted collection of circulating tumor cells (CTCs).
- Disease assessment (radiographic imaging) and re-staging revised and clarified.
- Made end of study (EOS) visit an end of treatment (EOT) visit instead.
- Study visit following last dose of onvansertib, previously referred to as the EOS visit, now renamed EOT visit.
- Definition of EOS (completion of study) consistently revised to once patients have been followed for 1 year after EOT rather than after last dose.

- Added additional information regarding follow-up (e.g., radiographic scanning, collection of new-anti-cancer treatment, defined patients to be followed as any ongoing from Phase 1b and all from Phase 2, etc).
- Deleted requirement that all AEs must be attributed to study drug unless there is a reasonably acceptable alternate cause for the AEs.
- In the event of defined toxicities, both the 5-FU bolus and/or leucovorin may be eliminated in subsequent cycles at the Investigator's discretion. Guidance was also provided if intolerance of individual drugs from the FOLFIRI + bevacizumab regimen is observed.
- Dose reductions for onvansertib were added. Dose delays for onvansertib were revised, including from patients who experience any Grade 2 or higher AE to any Grade 3 or higher AE considered related to the study drug will have their next dose of onvansertib withheld.
- Concomitant medications and treatments were clarified, and new prohibited medications added, and others deleted.

7.0 Study Objectives

Phase 1b:

To evaluate the Dose Limiting Toxicities (DLTs) and MTD and to select the Recommended Phase 2 Dose (RP2D) of onvansertib in combination with FOLFIRI (chemotherapy regimen of irinotecan, fluorouracil [5-FU], and leucovorin) and bevacizumab for treatment of histologically confirmed metastatic and unresectable Colorectal Cancer (CRC) in patients with a KRAS mutation who have failed or are intolerant of FOLFOX in the first-line setting.

Phase 2 part 1:

To assess the preliminary efficacy of onvansertib in combination with FOLFIRI and bevacizumab for treatment of histologically confirmed metastatic and unresectable CRC in patients with a KRAS mutation who have failed or are intolerant of FOLFOX in the first line setting for patients enrolled before protocol v2 with the eligibility criteria to confirm KRAS mutation through liquid biopsy.

Phase 2 part 2:

To assess the preliminary efficacy of onvansertib in combination with FOLFIRI and bevacizumab for treatment of histologically confirmed metastatic and unresectable CRC in patients with a KRAS mutation who have failed or are intolerant of FOLFOX in the first line setting for patients enrolled per the protovol v2 with the eligibility criteria not requiring confirming KRAS mutation through liquid biopsy.

8.0 Study Design

This is a multicenter, open label, single arm study to assess the safety and efficacy of onvansertib in combination with FOLFIRI and bevacizumab. One treatment cycle is 28 days.

Study population: Histologically confirmed metastatic and unresectable CRC in patients with KRAS mutation. Patients must have failed treatment with or be intolerant of FOLFOX given as first-line treatment for metastatic disease.

This study will consist of a Screening Period (within 28 days prior to the first dose of onvansertib), a Treatment Period conducted in 28-day cycles, EOT assessments, and a Follow-Up Period for up to 1 year after EOT. Completion of 1 year of follow-up constitutes completion of the EOS.

Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until Progressive Disease (PD) or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Patients will continue in follow up until **study completion** (defined as 1 year of follow-up after EOT), death, or withdrawal of consent for further follow-up. Patients may continue on treatment after radiographic progression if, in the judgment of the treating physician: the patient is benefitting from treatment; the patient has no ongoing Grade 2 or greater AEs that are attributed to study drugs; and there are no other therapies available for treatment of the patient's cancer.

8.1 Treatment Period: Phase 1b (Completed)

The completed Treatment Period of the Phase 1b portion of the trial enrolled patients in cohorts following a standard 3 + 3 dose-escalation design (Le Tourneau 2012). Patients orally received one of the onvansertib dose levels shown in **Table *1***. Patients also received FOLFIRI, and bevacizumab as outlined in **Table 2**. The starting dose level of onvansertib in the Phase 1b portion of the study was 12 mg/m^2/day for Days 1 to 5, and 15 to 19 of each 28-day cycle. Onvansertib was administered concurrently with FOLFIRI and bevacizumab.

Table 1 ***Dose Levels of Onvansertib in the Completed Phase 1b Portion of the Study***

Dose Level	Dose	Frequency
Dose level -2	3 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose level -1	6 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose level 0	12 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose level +1	15 mg/m^2 QD (found to be the MTD)	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose level +2	18 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle

Abbreviations: MTD = maximum tolerated dose; QD = daily.

Table 2 ***Dose of FOLFIRI and Bevacizumab in the Completed Phase 1b Portion of the Study***

Drug	Dose	Frequency
Bevacizumab	One dose of 5 mg/kg	Days 1 and 15 of each 28-day cycle
Irinotecan	One dose of 180 mg/m^2	Days 1 and 15 of each 28-day cycle
Leucovorin	One dose of 400 mg/m^2	Days 1 and 15 of each 28-day cycle
5-FU (bolus)[a]	One dose of 400 mg/m^2	Days 1 and 15 of each 28-day cycle
5-FU (infusion)	2400 mg/m^2	Beginning on Days 1 and 15 of each 28-day cycle: Continuous IV infusion for 46 hours

Abbreviations: 5-FU = fluorouracil; IV = intravenous.

[a] Dose modification including elimination of the 5-FU bolus infusion for Grade ≥2 neutropenia was allowed.

8.2 Treatment Period: Phase 2

The Phase 2 portion of the study commenced once the MTD/RP2D had been selected. The RP2D was chosen as the MTD which is defined as the highest dose at which 1 or fewer of 6 patients experienced a DLT during Cycle 1 of therapy in the Phase 1b portion of the study. The definition of DLT is provided in Section 10.8.3. Determination of the RP2D was based on evaluating all available data from the dose escalation Phase 1b portion of the study, including low-grade, but chronic toxicities, dose reductions, and/or missed doses of onvansertib. Based on results of the Phase 1b portion of this study, 15 mg/m^2/day was determined to be the MTD and was selected as the RP2D. The RP2D and dose modifications for onvansertib for the Phase 2 portion of the study are shown in **Table 3**. Patients will also receive FOLFIRI and bevacizumab in the Phase 2 portion of the study as shown in **Table 4**.

Table 3 ***Dose Modifications for Onvansertib in the Phase 2 Portion of the Study***

Dose Level	Dose	Frequency
RP2D	15 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose reduction 1	12 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle
Dose reduction 2	6 mg/m^2 QD	Days 1 to 5 and 15 to 19 of each 28-day cycle

Abbreviations: RP2D = Recommended Phase 2 dose; QD = daily.

Note: No dose reductions lower than 6 mg/m^2 are allowed, if needed the patient should be discontinued from study treatment.

Table 4 *Dose of FOLFIRI and Bevacizumab in the Phase 2 Portion of the Study*

Drug	Dose	Frequency
Bevacizumab[a]	One dose of 5 mg/kg	Days 1 and 15 of each 28-day cycle
Irinotecan	One dose of 180 mg/m^2	Days 1 and 15 of each 28-day cycle
Leucovorin[b]	One dose of 400 mg/m^2	Days 1 and 15 of each 28-day cycle
	Administration optional based on institutional guidelines and Investigator discretion	
5-FU (bolus)[a]	One dose of 400 mg/m^2	Days 1 and 15 of each 28-day cycle
	Administration optional based on institutional guidelines and Investigator discretion	
5-FU (infusion)	2400 mg/m^2	Beginning on Days 1 and 15 of each 28-day cycle: Continuous IV infusion for 46 hours

Abbreviations: 5-FU = fluorouracil; IV = intravenous.

[a] Or approved biosimilar.

[b] If the Investigator decides to eliminate the 5-FU bolus administration, they can also reduce the dose of leucovorin or eliminate leucovorin from the treatment regimen altogether per Investigator discretion and institutional guidelines.

8.3 Sample Size Considerations

This is a single-arm study that consists of determining the MTD and RP2D in the Phase 1b segment of the study and using the RP2D to treat patients in the Phase 2 continuation segment. The Phase 2 portion of the study has been amended to enroll additional patients at 15 mg/m^2 to obtain additional pharmacokinetic (PK), pharmacodynamic (PaD), preliminary sub-group PK cross-over food effect assessment, safety, and efficacy data for this dose and schedule of onvansertib given in combination with FOLFIRI + bevacizumab. The total sample size across both segments of the study is approximately 100 patients (18 patients in Phase 1b and approximately 80 patients in Phase 2).

8.3.1 Phase 1b

A standard 3 + 3 dose-escalation design was used (Le Tourneau 2012). The dose escalation scheme and DLT evaluation plan used is outlined in Section 3.1.2 of the protocol. The number of patients to be enrolled in Phase 1b was dependent on the observed safety profile, which determined the number of patients enrolled in each cohort. The total number of patients was expected to be up to 18 (and up to 6 patients per cohort).

8.3.2 Phase 2

In the Phase 2 portion of the study, patients will be enrolled and treated with 15 mg/m^2 (the RP2D, also the MTD, see Section 8.2) of onvansertib on Days 1 to 5 and 15 to 19 of a 28-day cycle concurrently with FOLFIRI + bevacizumab. The group of 6 patients who were enrolled at 15 mg/m^2 in Phase 1b will not be included in the primary analytic cohort for Phase 2 but will be used in selected secondary efficacy analyses.

The initial protocol used a null hypothesis of 5% ORR and an experimental hypothesis of 20% ORR for the onvansertib-containing regimen and determined that only 26 evaluable patients in Phase 2 were required to give the trial 90% power to detect improvement in ORR from 5% to 20% with a 10% Type I error rate. However, the trial is being expanded to include an adjusted null hypothesis of 15% against an expected ORR of 30%. Based on a one-sided binomial superiority one-sample test, assuming approximately 80 evaluable patients during Phase 2, with 2.5% Type I error, there will be at least 85% power to test the threshold ORR of 15% against the expected ORR of 30%.

8.4 Randomization

This is a single-arm study therefore no randomization is needed.

9.0 Study Endpoints

9.1 Phase 1b

- Characterization of the DLTs.
- Characterization of adverse events (AEs) by type, incidence, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0), seriousness and relationship to treatment.
- Effects on vital signs and laboratory parameters.
- Changes from baseline in electrocardiograms (ECGs), physical examinations, weight, and Eastern Cooperative Oncology Group (ECOG) performance status.

9.2 Phase 2 (part 1 and part 2)

9.2.1 Primary

Objective Response Rate (ORR, see Section 10.6.1) as determined by the investigators, using the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in patients who receive at least 1 cycle (28 days/4 weeks of treatment) of onvansertib in combination with FOLFIRI and bevacizumab ORR will be presented by the All-Treated Analysis set.

9.2.2 Secondary

The following secondary endpoints will be explored and will be conducted in the All-Treated Analysis Set:

- Disease Control Rate (DCR) defined as complete response (CR) plus partial response (PR) plus stable disease (SD)
- Safety, as assessed primarily by AEs, according to the NCI-CTCAE version 5.0 (conducted in the safety population consisting of all enrolled patients)
- Progression-free survival (PFS) defined from the date of first drug administration to progression or death, whichever occurs first
- Duration of response (DOR) defined from date of first response (CR or PR) to PD or death, whichever occurs first
- Overall survival (OS)
- Reduction in KRAS allelic burden on liquid biopsies
- PK of onvansertib in combination with FOLFIRI and bevacizumab

9.3 Exploratory

- Use of circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA) to evaluate relevant biomarkers correlated with patient response
- Use of (FFPE) tumor tissue to evaluate baseline genomic profiles (DNA/RNA) associated with patient response
- Preliminary sub-group PK cross-over food effect assessment

9.4 Analysis Sets

All Analysis sets mentioned below, will be summarized and listed per the actual dose level per the condition mentioned in each analysis set.

9.4.1 Safety Analysis Set

The safety analysis set is defined as patients who received at least one dose of onvansertib in any cycle. This analysis set will be used for demographic and safety analysis.

9.4.2 All-Treated Analysis Set

The all-treated analysis set is defined as patients who received at least 1 dose of assigned onvansertib in Cycle 1. This analysis set will be used for efficacy analysis. Patients who end treatment/study prior to the completion of the first cycle or not dosed with onvansertib in Cycle 1 will be excluded from this analysis.

The group of patients who were enrolled at 15 mg/m^2 in Phase 1b will be part of the primary and secondary efficacy analysis.

The all-treated analysis set is the same as the treated-patient population as mentioned in the protocol but worded differently for this SAP.

9.4.3 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) analysis set is defined as all patients in the safety analysis set who have at least one evaluable plasma concentration of onvansertib.

10.0 Conventions and Derivations

10.1 Study Day

All study days on or after the first administration of study treatment (onvansertib) will be calculated as:

Date of assessment – date of first administration of study treatment + 1.

Study days that occur before the first administration of study treatment will be calculated as:

Date of assessment – date of first administration of study treatment.

First onvansertib administration visit is considered as Study Day 1.
Every effort will be made to avoid missing and/or incomplete dates. In cases of missing and/or incomplete dates, study day will be missing.

10.2 Baseline

Unless specified otherwise, baseline will be defined as the last available measurement taken prior to the first administration of study treatment.

For applicable variables that include a date and time derivation, both date and time should be used in the calculations.

10.3 Change from Baseline

Change from baseline value is defined as the value at any given post-baseline time point minus the baseline value where both values are non-missing, i.e.,

Post-baseline value – baseline value.

10.4 Medical, Surgical or Procedure History

Past medical/surgical/procedure history is that with a stop date prior to the first administration of study treatment.

Current medical/surgical/procedure history is that with a start date prior to inclusion in the study but ongoing at the start date of the study treatment, i.e., ongoing on or after the first administration of study treatment.

For disease characteristics both time since CRC diagnosis and time since metastatic disease will be derived. For date of metastatic diagnosis, if patients had metastatic disease at diagnosis, then the date of metastatic disease is the same as the diagnosis date and the diagnosis date will be used for both derivations; if patients did not have metastatic disease at diagnosis and developed it later, then the date of diagnosis will be used to derive the time (in weeks) since diagnosis and the date of metastatic disease will be used to derive the time (in weeks) since metastatic disease.

10.5 Prior and Concomitant Treatment

Prior treatments are defined as treatments with a stop date prior to the first administration of study treatment.

Concomitant treatments are defined as treatments other than the study treatment that are ongoing or with a stop date on or after the first administration of study treatment.

Use of all prior and concomitant medications, including any change in treatment, will be recorded, categorized and summarized according to the latest version of the WHO Drug Dictionary. Each medication will be assigned a preferred term (PT).

Refer to Section 10.10.1 below for how to handle partial or missing dates in the assessment of whether a treatment was taken prior to or concomitantly with the study treatment.

10.6 Derivation of Efficacy Variable

Response will be based on Investigator assessment according to RECIST v1.1 (Eisenhauer 2009; Schwartz 2016) and will be reported using the following response categories: CR, PR, SD, PD and not evaluable (NE).

For each patient, the best overall response (**BOR**) is defined as the best overall response across all efficacy assessments, recorded from the start of treatment until first documented disease progression, or the date of start of subsequent therapy, whichever occurs first. BOR will be used to inform **ORR** (CR and PR).Radiographic imaging for disease restaging during the treatment period will be obtained prior to the start of Cycle 3 and all subsequent odd-numbered cycles (Cycles 5, 7, 9, etc), at EOT, and every 8 weeks thereafter until PD, start of a new anti-cancer therapy, or EOS, as indicated in the Schedule of Assessments in the protocol. Patients who are taken off onvansertib but remain on FOLFIRI + bevacizumab are not considered to have started a new anti-cancer therapy and should continue to undergo all study assessments as outlined in the Schedule of Assessments, including radiographic scans every 8 weeks. Radiographic imaging should include computed tomography (CT) of the chest/abdomen/pelvis with contrast (or magnetic resonance imaging [MRI] if patient has contraindication to intravenous contrast). CT is the preferred modality, but MRI is acceptable. The same imaging modality should be used for screening and for each disease reassessment scan.

10.6.1 Primary Efficacy

The primary efficacy measure in Phase 2 (part 1 and part 2) is ORR, which is defined as the percentage of patients documented to have a confirmed CR or PR using RECIST v1.1 (see Table 6 below), as determined by the investigator.

A Best Response of CR or PR, as shown Table 6 in below, cannot be assessed unless it is confirmed at the subsequent assessment (SD does not require confirmation provided that observation of SD occurs at least 8 weeks after start of study treatment).

Patients 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.

Table 6 ***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 patient is on-study for a minimum of 8 weeks. If the patient is on-study less than 8 weeks (56 ± 9 days), any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for patients where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for patients 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.

(4) For patients with unconfirmed CR/PR and who subsequently drop off the study, the best overall response will be SD.

10.6.2 Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of patients with BOR of CR, PR or SD, per RECIST v1.1.

10.6.3 Progression-free Survival

PFS is defined as the time in months from the date of first administration of study treatment until the first observation of PD or death due to any cause, whichever occurs first, i.e.,

(Date of first PD or death – date of first administration of study treatment + 1) / 30.4375

Refer to Section 10.6.6 for censoring rules.

10.6.4 Duration of Response

Duration of Response (DOR) is defined as the time in months from the first observation of a subsequently confirmed objective response (CR or PR) until the first observation of PD or death due to any cause in the absence of documented PD, i.e.,

(min (date of first PD, date of death) – date of first CR or PR + 1) / 30.4375

PD is the item 'Disease Progressing' captured on the Completion Status CRF page as a Reason for Discontinuation along with the associated date discontinued OR a disease response of PD as assessed by the investigator at the disease assessment evaluation.

DOR will only be calculated for the subgroup of patients achieving a confirmed CR or PR. Refer to Section 10.6.6 for censoring rules.

10.6.5 Overall Survival

OS is defined as the time in months from the date of first administration of study treatment until death due to any cause, i.e.,

(Date of death – date of first administration of study treatment + 1) / 30.4375

Refer to Section 10.6.6 for censoring rules.

10.6.6 Censoring Rules for Time-to-Event Endpoints

The following applies to the analysis of OS.

- For patients alive, censoring for survival will be done on the date of the last on study follow-up that the patient is reported to be alive or date of subsequent anti-cancer treatment/procedure. Patients who did not receive treatment or have no on-study data will be censored on the date of first administration of study treatment (Day 1).

The following censoring rules will apply to event dates for time-to-event endpoints that are based on radiographic evaluations, i.e., DOR and PFS:

- Endpoints will be censored on the date of the first dose of study treatment with duration of 1 day under the following scenarios (apply to PFS only):
  - Baseline disease assessment inadequate to apply RECIST1.1.
  - No disease assessments are performed during study treatment, except in the event of early death (see below for death as an event); or
  - All disease assessments performed during study treatment result in the conclusion of NE.
- Endpoints will be censored on the date of the last evaluable disease assessment under the following scenarios (apply to PFS and DOR):
  - PD or death occur after ≥2 consecutive tumor assessments that are missed or result in the conclusion of NE (i.e., > 16 weeks ± 1-week assessment window).
  - Patient administered alternative anti-cancer treatment/ procedure prior to documented PD.
  - Patient lost to follow-up.
  - Patient withdrawal of consent for follow-up; or
  - Patient continues study treatment without PD at the time of data cutoff or End of Study.

Date of death will be considered an event for DOR and PFS under the following scenarios:

- Death occurs prior to PD and ≤ 16 weeks + 1-week window after the first dose of study treatment.
- Death occurs ≤ 16 weeks + 1-week window after the last evaluable disease assessment; and

- Death in the absence of receiving subsequent anti-cancer treatment/ procedure.

10.7 Safety Variables

10.7.1 Treatment Related Adverse Event

The relationship of AE to study treatment is recorded as 'unrelated', 'unlikely', 'possibly', 'probably', or 'definite on the Adverse event record CRF pages will be presented for overall onvansertib treatment groups for each study drug treatment. All relationships categorized other than 'unrelated' and 'unlikely' will be classified as treatment related. If the relationship is not categorized or missing, it will be assumed to be related.

10.7.2 Treatment Emergent Adverse Event (TEAE)

AEs that occur or start or increase in severity on or after the first dose of study drug and no later than 30 days after the last dose of study drug will be considered treatment emergent.

The earliest date of the first dose of study treatment will be considered as the first dose date of the study treatment, and the latest date of the last dose of study treatment will be considered as the last dose date of the study treatment.

Refer to Section 10.10.1 below for how to handle partial or missing AE dates in the assessment of whether an event is TEAE.

The dose modification of the 5-FU bolus and leucovorin, occurrence of a Grade ≥ 2 neutropenia or neutropenic fever will be categorized with TEAE. On the CRF page 'Standard of Care Treatments' the answer to the question 'Was an AE the reason for 5-FU (bolus) not administered or modified? is captured at each visit. This question will be used together with the question 'Action Taken with Study Drug (5-FU Bolus)' on CRF page 'Adverse Event Record' to categorize each TEAE.

10.7.3 Dose Limiting Toxicity

Dose-limiting toxicities are defined as Grade 4 hematologic AEs, Grade ≥ 3 non-hematologic AEs that are considered related to the study drug and that do not resolve within 14 days following presentation with standard management and care, Grade ≥ 3 thrombocytopenia with bleeding, neutropenic fever, any death not clearly due to the underlying disease or extraneous causes, or any change in liver function that meets Hy's Law criteria of a DLT. A DLT would result in a hold of drug until the AE resolved to Grade 1 or less. The DLT must resolve within 2 weeks, or the patient will be discontinued from the study.

An AE with a response 'Yes' to the question "Is this Adverse Event considered DLT?" on the AE CRF page will be classified as a DLT, and an AE with a missing response to this question will also be classified as a DLT.

10.7.4 Most common occurring TEAEs

Most common occurring TEAEs are the AEs that are occurring in ≥10% of patients.

10.7.4.1 Hy's Law

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × ULN concurrent with an increase in total bilirubin to ≥ 2 × ULN (upper limit of normal) but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's Law and raises the concern for drug-induced liver injury when no other cause is identified.

10.7.5 Clinical Laboratory Parameters

Clinical laboratory parameters to be collected routinely on study are detailed in the protocol's schedule of assessments table. All parameters will be tested by local laboratories. Clinical laboratory data will be entered into the electronic data capture (EDC) system and converted to International System (SI) units for analysis. Normal ranges (provided by Cardiff) will be merged in during dataset programming. Baseline

laboratory parameters are the last collected any time prior to start of treatment on Cycle 1 Day 1 in each phase.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after the first administration of study treatment or that are present at baseline and worsened following the first administration of study treatment are included as AEs or Serious Adverse Events (SAEs).

10.7.6 Physical Examination and Vital Signs

Abnormal results of physical examinations of body systems will be captured on the Medical History CRF pages (at screening examinations) and the Adverse Events CRF pages (after screening examinations).

The vital signs collected on this study are height (cm), weight (kg), Body mass index (BMI) (kg/m^2), BSA (m^2), body temperature (°C), systolic and diastolic blood pressure (mmHg), pulse (beats/min), and respiratory rate (breaths/min). These will be entered on the Vital Signs – Screening and Vital Signs CRF pages. Baseline vital signs are the last collected any time prior to start of treatment on Cycle 1 Day 1 in each phase.

10.7.7 Electrocardiograms

Triplicate 12-Lead ECGs will be performed at scheduled time points as indicated in the Schedule of Assessments in the protocol, and the following information will be entered on relevant CRF pages:

- mean heart rate (beats/min)
- mean QT interval (msec)
- mean QTc (msec) by the Fridericia's formula, QTcF
- mean PR interval (msec)
- mean QRS interval (msec)
- indicator of clinically significant ECG

Categories for QTcF are described as below:

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

Categories for change from baseline in QTcF are described as below:

- ≤ 30 msec
- > 30 to ≤ 60 msec
- > 60 msec

Baseline values are the most recent reported measurements prior to start of treatment on Cycle 1 Day 1 in each phase.

Any clinically significant changes in ECGs that occur during the study should be reported as an AE on relevant CRF pages.

10.7.8 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (grade or score ranging from 0-5) will be collected at scheduled time points as indicated in the Schedule of Assessments and reported on the ECOG performance status CRF pages.

10.8 Other Derived Variables

10.8.1 Body Mass Index

BMI will be calculated based on baseline weight and baseline height using the following formula:

$$BMI = Weight\ (kg) / Height\ (m)^2$$

10.8.2 Body Surface Area

Body mass index (BSA) will be calculated based on baseline weight and baseline height using the following formula:

$$BSA\ (m^2) = 0.007184 * weight^{0.425} * height^{0.725}$$

10.8.3 Age

Age in years is calculated using baseline information and demographics recorded on relevant CRF pages, i.e.,

(Date of informed consent signed – Date of birth) / 365.2425

In addition to being analyzed as a continuous variable, baseline age will be categorized into the following groups:

- < 65 years old
- 65 to 75 years old
- > 75 years old

10.9 Handling of Partial or Missing Dates

For calculating durations there will be no imputations made for partial or missing dates. Where duration of an event is calculated based on actual dates and any of the dates used in the computational algorithm are partial or missing, the duration will also be missing.

For assigning medical histories as 'past or current', AEs as 'treatment-emergent' and therapies as 'prior or concomitant', (partially) missing start and stop dates will not be imputed.

In general, an AE will be considered treatment-emergent, unless there is evidence in the (partial) dates available that it was not treatment-emergent. In cases of missing start dates of AEs, these will be considered treatment-emergent, unless the stop date of the AE is prior to the first administration of study treatment. In the case of partially missing start dates, the AE will be considered treatment-emergent, unless the information from the partial dates clearly shows that the AE was not treatment-emergent.

In general, medical histories, surgeries or procedures will be considered current unless there is evidence in the (partial) stop dates or complete stop dates available that the medical history, surgery or procedure was stopped prior to the first administration of study treatment.

The same rules will be applied to partial or missing diagnosis dates as given below.

10.9.1 AE and Concomitant Medication Partial Start and Stop Dates

The following rules will be applied to impute missing start and stop dates in appropriate data types (e.g., AEs or concomitant medications):

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 medication.

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 below procedure.

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

- If the stop date is completely missing, then it will be imputed with the latest of the study discontinuation date, study completion date or date of last contact in the study.

- If the patient died and if the imputed stop date is greater than the death date, then the imputed stop date will be set to the death 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.
- 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 below procedure.

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 **last visit date** will be assigned to the missing fields.

10.9.2 Partial Dates of Diagnosis, Disease History and Death

The partial start date for diagnosis of metastatic disease and prior disease history will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing).

If a death date is missing month or day, the following imputation method will be used:

- If only the death year is known and the last date the patient was known to be alive is in the same year, the patient's last alive date will be used as the death date. If the last alive date occurs in a previous year, the missing death month and day will be imputed as the first day and month of the year (01JAN).
- If the year and month are known and the last alive date is in the same year and month as the death date, then the last alive date will be used. If the last alive date is in a month prior to the death month, then the death day will be imputed as the first day of the month.

10.10 Handling of Missing Adverse Event Severity and Relationship

If Severity is missing the event will be queried to site and missing values will be completed. If relationship is still missing the event will be assumed to be related.

10.11 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.

10.12 Handling of Unscheduled Visits and Unscheduled Assessments

Generally, data collected at unscheduled visits will be included and analyzed if they are in the visit window (protocol schedule of assessments), closest to the scheduled visit. If 2 values are the same distance to the target day of the scheduled visit (1 value before and 1 after), then the latest value will be selected as analysis value. In case of multiple values collected on different dates but are in range of the scheduling window of the target visit, then the latest value will be selected. In case of latest collected time point 2 or more values collected on the same date, then for continuous data, the average among the results will be derived and for categorical data, the clinically 'worse' (Grade 3 vs Grade 2) value will be selected.

10.13 End of Treatment

EOT evaluation should occur within 28 days (± 5 days) of the last administered dose of onvansertib. Patients who complete EOT form declaring discontinuation due to any of the reasons.

10.14 Follow-Up and End of Study

Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for OS for 1 year after EOT (alive versus deceased with dates). Patients who are taken off onvansertib but remain on FOLFIRI + bevacizumab or any component(s) of the FOLFIRI + bevacizumab regimen will also continue follow-up for radiographic disease progression via CT/MRI scans every 8 weeks. Follow-up information regarding new anticancer treatment, such as type of treatment and duration of treatment, will be collected approximately every 8 weeks during the 1-year follow-up period. Once patients have been followed for 1 year after EOT, they will be considered to have completed the study (EOS).

11.0 Interim Analyses

There is no formal interim analysis planned for this study.

12.0 Statistical Methods

All data collected during the study will be presented in data listings unless otherwise specified. Data listings will be sorted by dose and patient. Screen failures will be excluded from all tables and listings except those summarizing screen failures or patient disposition.

Descriptive summaries will be tabulated by their initially assigned dose levels and overall and presented for each phase. Patients who have intra-patient dose escalation will be summarized in the dose level cohort they received on Cycle 1 Day 1. PK summaries will not include the total overall dose levels.

Categorical data will be presented using counts and percentages, with the number of patients in each dose level category as the denominator for percentages. 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. Missing data will be summarized by counts only.

Continuous data will be summarized using the number of observations (n), number of missing values, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum. Minimum and maximum will be rounded to the precision of the original value. Mean and median will be rounded to 1 decimal place more than the precision of the original value. The SD will be rounded to 2 decimal places more than the precision of the original value, up to a maximum of 3 decimal places.

Unless otherwise specified, missing data will not be imputed.

All statistical analyses will be performed using SAS® Version 9.4 or higher.

12.1 Patient Disposition

In all analyses, patients will be grouped by dose level cohorts according to their initial dose level assignment and presented for each phase.

The number of patients screened, enrolled, the number and percentage of patients treated in the study and in each of the analysis sets will be summarized. For all Enrolled patients, the number and percentage of patients having completed or prematurely discontinued each study drug treatment and/or withdrawn from the study will be presented along with a breakdown of the corresponding reasons for withdrawal and/or discontinuation. The same will be summarized also for patients enrolled at each site based on patients enrolled to this study.

Enrollment information such as date of informed consent, details pertaining to dose level assignments, date of last study treatment, date of completion of study and reasons for withdrawal and/or discontinuation will be presented in listings. Details for analysis sets to which they belong will also be presented in listings for all Screened patients.

12.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics, but no formal statistical tests will be performed. Demographics and baseline characteristics including age (years), age categories, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2) and BSA (m^2) will be summarized at baseline using the Safety Analysis Set. These data will also be listed.

Baseline characteristics including ECOG performance status, The number of weeks from CRC diagnosis to the first dose of study drug, number of weeks since metastatic disease to the first dose of study drug, number of weeks from disease progression qualifying for this trial to the first dose, TNM (Tumor, lymph Nodes, Metastasis) Staging at Diagnosis (primary tumor, regional lymph nodes, distant metastasis and Location of Primary Tumor) Metastasis at diagnosis and KRAS Mutation, will be summarized for the safety analysis set.

12.3 Treatments

All study treatments will be summarized and listed by Safety Analysis Set. Following parameters will be summarized:

12.3.1.1 Duration of Exposure

Duration of exposure (weeks) is defined as: (Date of last administration of study treatment – date of first administration of study treatment + 1) / 7

12.3.1.2 Number of Cycles

The number of cycles is defined as the number of treatment periods, regardless of length, that are repeated on a regular schedule, where the study treatment is initiated or re-initiated with an administration of at least one dose.

12.3.1.3 Number of Treatment Delays

The number of patients with delay in the study drug treatment. This is flagged by "Drug Interrupted" under "action taken with study drug" of the AE page captured on the CRF. This is presented for each study drug treatment (Onvansertib, Bevacizumab, Irinotecan, Leucovorin, 5-FU Bolus and 5-FU Infusion) for overall treatment level of Onvansertib.

Descriptive statistics of the number of patients with at least one treatment delay will be presented.

12.3.1.4 Patients with Treatment Discontinuation

The number of patients that discontinued the treatment. This is flagged by "Drug Withdrawn" under "action taken with study drug" of the AE page captured on the CRF. Descriptive statistics of the number of patients with at least one treatment discontinuation will be presented,

12.3.1.5 Patients with Dose Adjustment

A dose adjustment for Onvansertib is defined as any change in the dose assigned for administration. Dose adjustments of study treatment are captured as Actual Dosing Level as compared against Protocol Assigned Dosing Level on the Onvansertib Dosing Information CRF pages. The counts and percentages of patients with adjusted dose will be presented by dose level and overall.

12.3.1.6 Total Dose Administered

Total dose administered is defined as the total amount of study treatment doses received and recorded as 'Actual dose given' on the Onvansertib Dosing Information CRF pages, i.e., sum over all available actual doses recorded in mg. For other drugs the total dose will be all doses administered (mg) on Standard of Care treatment CRFs.

12.3.1.7 Patients with Missed Doses

A missed dose is defined as any planned dose not administered that is captured as a 'No' response to the field 'Did the patient dose on site?', and 'No' to 'Did the patient take the prescribed dose for the cycle day x?*Did the patient take all doses as prescribed on days 1-5 and 15-19?', and any non-missing value entered into the field 'Reason prescribed dose not administered' on the relevant Onvansertib Safety Variables.

12.3.1.8 Dose Intensity

Relative Dose Intensity (%) will be calculated as:

- Relative Dose Intensity (%) = (cumulative dose actually received in mg / cumulative dose planned in mg) * 100
- Cumulative dose planned = sum of planned doses (mg) in all completed cycles
- Cumulative dose actually received = sum of actual doses (mg) in all completed cycles

12.3.1.9 Compliance

Compliance is calculated as:

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

For onvansertib the number of planned doses is the number of treatment cycles x 10. For other drugs the number of planned doses is the number of treatment cycles.

12.3.2 Extent of Study Drug Exposure

Onvansertib exposure in combination with FOLFIRI and Bevacizumab will be summarized for the following parameters:

- Duration of exposure (Weeks)
- Number of cycles administered

- Number of Treatment delays
- Number of Treatment discontinuations
- Patients with dose adjustments
- Total dose administered
- Patients with missed doses
- Relative Dose Intensity
- Compliance

FOLFIRI and Bevacizumab exposure in combination with Onvansertib will be summarized for the following parameters:

- Duration of exposure (weeks)
- Number of cycles administered
- Number of Treatment delays

A listing will present exposure data by patient for study treatment administration for the safety analysis set. Separate listings will present exposure data for FOLFIRI, and bevacizumab administration based on the safety analysis set.

12.3.3 Prior and Concomitant Treatments

All past and current medical, surgical or procedural history will be summarized by the safety analysis set using MedDRA (Medical Dictionary for Regulatory Activities) dictionary. The prior and concomitant medications will be summarized by the safety analysis set using the WHODrug dictionary. The number and percentage of patients using at least one prior or concomitant treatment will be summarized along with the count and percentage of patients using at least one prior or concomitant treatment for each PT. Also, the prior chemotherapies will be summarized for any chemotherapy received, number of cycles of chemotherapy and chemotherapy toleration.

All prior and concomitant medications and procedures will also be listed for the safety set and will be classified as prior or concomitant.

12.4 Protocol Deviations

Protocol deviations will be summarized and listed by the safety analysis set. Major protocol deviations will be summarized by deviation category. Data listing will present all protocol deviations by patient including whether deviation is an important protocol deviation.

12.5 Safety Analyses

The primary safety endpoints are type, incidence, severity, seriousness and relationship to treatment of AEs evaluated until the end of study and change from baseline in the parameters of vital signs, laboratory in blood and urine, physical examination, ECGs, weight, ECOG performance status and biomarker in blood. Continuous and categorical safety data will be summarized separately.

Inferential statistical analysis comparing the safety data among study treatment dose levels is not planned.

12.5.1 Adverse Events

Safety will be assessed primarily based on AEs. All summaries of AEs will be based on treatment-emergent AEs (TEAEs) unless otherwise indicated. TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), according to severity as per NCI-CTCAE version 5.0.

A breakdown of the number and percentage of patients reporting each TEAE, categorized by SOC and PT coded according to the MedDRA dictionary and the maximum severity graded according to the NCI-CTCAE

guidelines, will be presented. Note that counting of AEs will be by patient not event and patients are only counted once within each SOC or PT.

Listings of TEAEs, Treatment-Emergent SAEs, TEAEs leading to discontinuation, TEAEs leading to discontinuation of study treatment, TEAEs with the outcome of death will also be provided. If an AE is coded using more than one PT for a single Verbatim Term (VT), then the PTs will be grouped together within the same VT line for the listings only.

A summary of Treatment-Emergent SAEs, categorized by SOC and PT will be presented. Note that counting will be by patient not event and patients are only counted once within each SOC or PT category.

The number and percentage of patients who report AEs and the number of events will be summarized by dose cohort and presented for each phase for the safety analysis set as in the following:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- Most common occurring TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum NCI-CTCAE grade
- TEAEs that are DLTs by SOC and PT and maximum NCI-CTCAE Grade
- TEAEs related to study treatment by SOC, PT, and maximum NCI-CTCAE grade
- NCI-CTCAE Grade ≥ 3 TEAEs by SOC and PT
- NCI-CTCAE Grade ≥ 3 TEAEs related to study treatment by SOC and PT
- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT and NCI-CTCAE Toxicity Grade
- Serious TEAEs related to study treatment by SOC, PT, and NCI-CTCAE Toxicity Grade
- TEAEs leading to study discontinuation by SOC, PT and maximum NCI-CTCAE grade
- TEAEs related to study treatment leading to study discontinuation by SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to any dose discontinuation by SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to study treatment dose discontinuation SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to any dose reduction by SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to study treatment dose reduction by SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to any dose interruption by SOC, PT and maximum NCI-CTCAE grade
- TEAEs leading to study treatment dose interruption by SOC, PT and maximum NCI-CTCAE grade
- TEAEs with an outcome of death by SOC and PT

For grade summaries, patients with multiple events within a particular SOC or PT category will be counted under their most severe event within that SOC or PT category. Events will be sorted by descending frequency of the total across all dose cohorts by SOC, and by PT within SOC for summaries.

AEs and TEAEs will be listed for individual patients, including information regarding onset, duration, severity, seriousness, relationship to study treatment, outcome and actions taken.

12.5.2 Deaths

AEs with an outcome of death will be listed. In addition, deaths collected on the Follow Up Visit CRF page will be presented in a listing.

12.5.3 Laboratory Data

Laboratory results will be presented in shift tables as well as continuous summaries. For hematology, parameters will include neutrophils, platelets and White Blood Cells (WBC). CEA will be the only clinical chemistry parameter summarized. The time points included in the summary tables will be collection times as specified in the schedule of assessment (refer to protocol section 6.1).

Shift tables will be provided for the maximum post-baseline grade including data from any unscheduled post-baseline time point, and the last study assessment while on study treatment. These tables will compare the NCI-CTCAE grade for the baseline value relative to each post-baseline time point value for all non-missing post-baseline data. NCI-CTCAE grading will be done programmatically for the list of the following lab tests:

Lab Test Name	CTCAE Term
Clinical Chemistry	
Sodium (High values)	Hypernatremia
Sodium (Low values)	Hyponatremia
Potassium (High values)	Hyperkalemia
Potassium (Low values)	Hypokalemia
Bicarbonate (Low values)	Blood bicarbonate decreased
Calcium* (High values)	Hypercalcemia
Calcium* (Low values)	Hypocalcemia
Magnesium (High values)	Hypermagnesemia
Magnesium (Low values)	Hypomagnesemia
Phosphorus (High values)	Hyperphosphatemia
Creatinine (High values)	Creatinine increased
Glucose (Low values)	Hypoglycemia
Albumin (Low values)	Hypoalbuminemia
Alkaline phosphatase (High values)	Alkaline phosphatase increased
Total bilirubin (Low values)	Blood bilirubin increased
AST (High values)	Aspartate aminotransferase increased
ALT (High values)	Alanine aminotransferase increased
Hematology	
Eosinophils, absolute	Eosinophilia
Hemoglobin (HGB) (Low values)	Anemia
Hemoglobin (HGB) (High values)	Hemoglobin increased
Lymphocytes, absolute (Low values)	Lymphocyte count decreased
Neutrophils, absolute (Low values)	Neutrophil count decreased
Platelet count (Low values)	Platelet count decreased
White blood cells (WBC) (High values)	Leukocytosis
White blood cells (WBC) (Low values)	White blood cell decreased

12.5.4 Vital Signs

A summary of abnormal vital signs by time points and change from baseline will be presented. A summary of clinically important vital signs will also be presented where abnormal vital signs are systolic blood

pressure >140 mmHg, diastolic blood pressure >90 mmHg, pulse rate <60 bpm or >100 bpm, or temperature >37.5°C.

Vital sign results will be provided in data listings.

12.5.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Additional safety assessments include physical examinations, ECG measurements, ECOG performance status and, pregnancy tests.

Summaries of the above safety assessments are described below. Only listings will be generated for physical examination and pregnancy test results.

12.5.5.1 ECG

A summary of average of triplicate 12-lead ECG parameters, heart rate, QT interval, QTcF interval and change from baseline will be presented for each planned visit.

The number and percentage of patients who have abnormal QTcF during the study will be summarized by the following International Conference on Harmonization (ICH) E14 categories:

- QTc interval <=450 msec
- QTc interval >450 and<= 480 msec
- QTc interval > 500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline <=30 msec
- QTc interval >30 and <=60 msec from baseline
- QTc interval increases from baseline > 60 msec

All triplicate and average ECG data will be provided in data listings.

12.5.5.2 ECOG Performance Status

For Phase 1b and Phase 2, shift table comparing ECOG baseline score to maximum post-baseline score will be presented.

All ECOG data will be provided in data listings.

12.6 Efficacy Analyses

Patients from the All-Treated Analysis Set will be included in the efficacy analyses.

Patients enrolling after protocol v2, will be categorized under Phase 2 part 2 due to change in the Inclusion/ Exclusion criteria while the patients enrolled in Phase 2 before the protocol v2 will be categorized under Phase 2 part 1.

Primary and secondary efficacy summaries will be generated for Phase 2 (separately, for part 1 and part 2) patients. Derived efficacy data for Phase 1b and Phase 2 patients will be presented in patient listings. Inferential statistical analysis comparing efficacy data among study treatment dose levels or against historical data is not planned.

12.6.1 Objective Response Rate

The primary efficacy measure is ORR in Phase 2 patients as defined in section 12.6.ORR will be conducted for confirmed CR or PR results. Patients without efficacy evaluable assessments will be non-responders in the All-Treated Analysis Set.

The number and percentage of Phase 2 patients achieving ORR, CR, PR, SD or PD will be summarized and tabulated based on the All-Treated Analysis Set.

ORR will be summarized for the All-Treated Analysis Set with the Exact Clopper-Pearson 95% confidence intervals (CIs) presented, by which the comparison against a historical baseline response rate or comparison with other currently approved treatments can be made.

A waterfall plot of maximum percent change in sum of Target lesions for each patient with their respective treatment group will be presented.

A swimmer plot of patients' response over time for each treatment group will be presented.

A Spider plot for Tumor response of patients with percent change from baseline measurements over time will be presented.

Response data will also be presented in listings.

12.6.2 Duration of Response

DOR will be summarized using Kaplan-Meier (KM) estimates for the All-Treated Analysis Set who have had a confirmed response (confirmed CR or PR). The, 25%, 50%, and 75% quartiles will be presented with associated 95% CIs for the quartiles using the KM method, and the survival rate at 3, 6, 9 and 12 months with associated 95% CI will be presented. A KM plot will be presented. The number of patients at risk in each dose level at each time point will be shown on the plot.

DOR data will also be presented in listings.

12.6.3 Progression-free Survival

PFS will be analyzed in the same way as for DOR.

12.6.4 Overall Survival

OS at 12 months will be estimated using the same approach as for duration of response as mentioned in section 12.6.2.

12.6.5 Subgroup Analysis

Efficacy analyses will be repeated for the following subgroups:

- By primary tumor localization: Right colon or non-right colon (left colon, rectal and other CRC)
    - Summary table and Kaplan-Meier plot for PFS and OS will be provided
- By bevacizumab in the first line treatment: Yes or No
    - Bevacizumab in first line treatment is defined as the Bevacizumab treatment done in prior chemotherapies
    - Summary table and Kaplan-Meier plot for PFS and OS will be provided
- Number of metastatic organs: One or (two or more)
    - Metastatic organs are the organs which are not in colon or rectum on target and non-target lesion eCRF (Electronic Case Report Form) pages of baseline/screening
    - Summary table and Kaplan-Meier plot for PFS and OS will be provided
- Baseline tumor measurement (sum of the longest diameters of the target lesions): ≤median versus >medianvalue (exploratory only)
    - Median tumor measurement is the median baseline tumor value across all the patients.
    - Summary table and Kaplan-Meier plot for PFS and OS will be provided
- KRAS Mutant Allelic Fraction (MAF):
    - Percent change from Cycle 1 Day 1 to Cycle 2 Day 1 ≤median versus >median KRAS MAF (KRAS mutant allele fraction) median value (exploratory only)

- Percent change from Cycle 1 Day 1 to Cycle 2 Day 1 for objective response (Yes versus No)
- Disease control rate percent change from Cycle 1 Day 1 to Cycle 2 Day 1 for ≤median versus >median KRAS MAF median value
- Objective response for KRAS MAF reduction from Cycle 1 Day 1 to Cycle 2 Day 1 for ≤90% versus >90%

12.6.6 Changes in KRAS Allelic Burden on Liquid Biopsies

Change from baseline KRAS mutant allelic burden at cycle 2 day 1 based on liquid biopsies will be summarized for the following:

- Change from baseline measurement to cycle 2 day 1
- Based on objective response (Yes/No)
- ≤median versus >median KRAS MAF median value from Cycle 1 Day 1 to Cycle 2 Day 1
  - PFS, DOR
- ≤90% versus >90% KRAS MAF reduction from C1D1 to C2D1
  - ORR, PFS, DOR
  - Kaplan-Meier plot for DOR, PFS and Waterfall plot for change in KRAS MAF reduction will be provided

These will be tabulated and listed for the All-Treated Analysis Set. Data will be obtained and transferred during the study. This shall be detailed in a separate analysis plan.

12.6.7 Exploratory Efficacy Analyses

These are outside the scope of this SAP.

12.7 Pharmacokinetic Analyses (PK)

PK summaries will be presented by Pharmacokinetic Analysis set. PK timepoint collection changed from protocol v1.4 and v2.0, refer both protocols for details.

Per protocol v2.0, PK assessments are conducted on Day 1 (pre-dose) and Day 5 (2-4 hours post dose) of Cycles 1,3 and 5.

Per protocol v1.4, PK assessments are conducted only for Cycle 1 for days 5,6,7 and 8. On Day 5, sample are collected pre-dose and 1,2,3,4 and 8 hours post dose. Samples on days 6,7 and 8 are collected 24, 48 and 72 hours post dose (Day 5).

PK concentration summary will present concentrations for samples collected per both protocol v1.4 and v2.0.

PK parameters summary will present only parameters for samples collected per protocol v1.4.

12.7.1 Pharmacokinetic Variables

Concentrations of study treatment will be collected in plasma.

PK parameters of study treatment will be calculated for plasma.

12.7.2 Plasma Pharmacokinetic Summaries

12.7.2.1 Plasma Concentrations

The lower limit of quantification (LLOQ) of onvansertib is 0.100ng/mL. Plasma concentrations of onvansertib below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values and will be excluded from the parameters from the natural log transformation. Descriptive statistics (number of patients, mean, geometric mean, standard deviation (SD), coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by phase, cycle and planned dose at each scheduled time point.

Linear (+SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling times will be provided by phase, cycle and dose. These plots will show time in hours. The plots will present all calculated means and will include a reference line for LLOQ.

All individual patient plasma concentration data will be listed by patient, by phase and dose.

12.7.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for onvansertib will be estimated using non-compartmental methods with WinNonlin® version 8.1 using the Best Fit regression to estimate the half-life. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

In estimating the PK parameters, BQL values at the beginning of the profile will be set to 0. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the PK specialist.

The plasma concentration of onvansertib administered in combination with FOLFIRI and bevacizumab will be collected at specified study time points measured according to the Schedule of Assessments in protocol, and reported by time points for onvansertib. The following PK parameters will be calculated as applicable for each patient:

Table 7. PK Parameters

Parameter	Description	SAS Programming Notes
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WinNonlin
Ctrough	Observed plasma concentration at the end of each dosing interval	Pre-dose concentration for Cycle 1, 3, 5 from ADPC. Calculated in SAS.
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WinNonlin
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration). Patient 017 will not pe presented in the outputs for this parameter as this patient has concentration samples for only 4 hours making the result unreliable.	AUClast from WinNonlin

Parameter	Description	SAS Programming Notes
AUCtau	Area under the concentration-time curve over the dosing interval (time 0 to 24hr). If the nominal 24hr concentration was taken at or after 24hr postdose then AUCtau will be calculated by WinNonlin to 24hr. If the nominal 24hr concentration was taken before 24hr post-dose and a valid λz is available, then the data will be extrapolated to 24hr. If the nominal 24hr concentration was taken before 24hr post-dose and a valid λz is not available, then AUC0-24 calculated to actual time will be used for AUCtau.	AUClast from WinNonlin AUCtau from WinNonlin In case when AUCtau might not be available in WinNonlin file, summary file might be used to extract the parameters for 24h nominal sampling time
T-HALF	Terminal phase half-life expressed in time units	HL_Lambda_z from WinNonlin
CLss/F	Apparent clearance at steady state	CLss_F from WinNonlin
Vss/F	The apparent volume of distribution during the terminal phase is calculated by dividing Dose by the product of AUCtau and Lz.	Vz_F from WinNonlin

Descriptive statistics (number of patients, mean, geometric mean, SD, %CV, median, min, and max) will be used to summarize the calculated PK parameters by phase, cycle and planned dose. For Tmax, only median, min and max will be presented.

All parameters will be listed by patient, phase, cycle and dose.The following parameters will be used for diagnostics and thus listed but not summarized.

Parameter	Description	SAS Programming Notes
Adjusted R Squared	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of Lz.	Rsq_adjusted from WinNonlin
Lz	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Using no weighting factor, the terminal log- linear phase of the concentration-time curve is identified by least-square linear regression of at least 3 data points that yielded a maximum G criteria, which is also referred to as adjusted R^2. Lz is the absolute value of the slope of the terminal log-linear phase. Note: In Phoenix, use Best Fit method to determine regression.	Lambda_z from WinNonlin

12.7.3 Food Effect

Food effect analysis is outside the scope of this SAP. The data collected for food effect analysis will only be listed.

12.8 Pharmacodynamic and Diagnostic Biomarkers

ctDNA isolated from blood samples will be used to monitor changes in KRAS mutant allelic frequency (MAF), and to evaluate relevant biomarkers correlated with patient response. CEA will also be collected to evaluate correlation between CEA and other biomarkers as well as correlation with radiographic response.

Tumor tissue will be used to evaluate baseline genomic profiles (DNA/RNA) associated with patient response.

Exploratory PaD analysis will include assessments of PaD biomarkers in both blood and tumor tissue. The relationship between onvansertib concentration and selected efficacy and safety outcomes may be explored. The correlation between biomarkers and clinical outcomes may be analyzed. In addition, exploratory analyses aimed at evaluating the relationship between drug concentration and changes in ECG parameters will be provided. Additional exploratory PK and PaD analyses may be conducted as appropriate but not in the scope of this SAP.

12.9 Methods for Handling Dropouts and Missing Data

In Phase 1b, patients who are discontinued prior to completing the first treatment cycle for any reason other than toxicity, or who have not received at least 80% of the intended doses without experiencing a DLT will be replaced. Data for patients who are replaced will not be included in the summary analyses; data for replaced patients will be presented in data listings.

Sensitivity analyses of response parameters including all patients (with replaced patients analyzed as non-responders) may be generated as deemed appropriate per study results. Censoring rules for time to event endpoints are specified in previous sections. Rules for imputation of missing/partial dates and other missing data are also specified in previous sections.

12.10 Multiplicity

There will be no adjustment made for multiplicity as there are no formal statistical tests planned.

12.11 Impact by COVID-19

A sensitivity analysis may be carried out at the end of the study if the number of patients impacted by the COVID-19 pandemic is large (e.g., >10% missed a dose or assessment due to COVID-19) and thought to be impacting the safety and efficacty endpoints. This sensitivity analysis may exclude the patients affected by the pandemic.

13.0 References

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Le Tourneau C, Gan HK, Razak AR, Paoletti X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. PLoS One. 2012;7: e51039.

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
5-FU	Fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration)
AUCtau	Area under the serum concentration-time curve over the dosing interval (time 0 to 24hr)

BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
BQL	Below the Quantifiable Limit
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CLss/F	Apparent clearance at steady state
Cmax	Maximum plasma concentration
CR	Complete Response
CRC	Colorectal Carcinoma
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
Ctrough	Observed plasma concentration at the end of each dosing interval
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECOG	Easter Cooperative Oncology Group
EOS	End of Study
EOT	End of Treatment
FFPE	Formalin-fixed, paraffin-embedded
FOLFIRI	Chemotherapy regimen for treatment of colorectal cancer made up of the drugs Folonic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F" and irinotecan (Camptosar) "IRI"
FOLFOX	Chemotherapy regimen for treatment of colorectal cancer made up of the drugs Folinic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F" and Oxaliplatin (Eloxatin) "OX"
HGB	Hemoglobin
IV	Intravenously
KM	Kaplan-Meier
KRAS MAF	KRAS mutant allele fraction
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging

MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OS	Overall Survival
PaD	Pharmacodynamic
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
QTcF	QT interval with Fridericia's correction
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation/Stable Disease
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, and Listings
T-HALF	Terminal phase half-life expressed in time units
Tmax	Time to maximum plasma concentration
TNM	Tumor, lymph Nodes, Metastasis
TPR	Time Point Response
ULN	Upper Limit of Normal value
Vss/F	The apparent volume of distribution
VT	Verbatim Term
WBC	White Blood Cell count
WHO	World Health Organization