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

Document Date: 27 October 2021

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

[redacted]

Protocol Amendment 1, dated 26 Oct 2021

Summary of Changes with Protocol Amendment 1, dated 26 Oct 2021

CLINICAL STUDY PROTOCOL

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 Number:	TROV-054
Study Phase:	1b/2
Product Name:	Onvansertib (also known as PCM-075)
IND Number:	141701
Sponsor:	Cardiff Oncology, Inc. 11055 Flintkote Avenue San Diego, CA 92121 Phone: [redacted] Email: [redacted]
Issue Date:	26 Oct 2021
Version Number:	2.0

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

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PROTOCOL APPROVALS

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 APPROVAL SIGNATURES
Cardiff Oncology, Inc.

[redacted]

[redacted]
Signature

[redacted]
Title

10/27/2021
Date

[redacted]

[redacted]

[redacted]
Title

10/27/2021
Date

INVESTIGATOR SIGNATURE PAGE

Protocol No: TROV-054
Protocol Version: 2.0
Protocol Date: 26 Oct 2021
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**

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the Clinical Study.

I will provide copies of the protocol to the Investigational Review Board and all members of the Study team responsible to me who participate in the Study. I will discuss this material with them to ensure that all participating personnel at the Study site are fully informed regarding the investigational drug and the conduct of the protocol.

Once the Investigational Review Board (IRB) approves the protocol, I will not modify this protocol without obtaining the prior approval of both the Sponsor and the IRB. I will submit the protocol modifications and/or any modifications to the Informed Consent Form to the Sponsor and the IRB, as applicable, and approval will be obtained before any modifications are implemented.

Investigator's Signature	Date
Investigator's Printed Name	
Study Site Name	
Address	
City, State, Zip Code, Country	

SYNOPSIS

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 Number:	TROV-054
IND Number:	141701
Number of Study Sites:	This study will be conducted at approximately 7 study centers in the United States.
Phase:	1b/2
Principal Investigator:	[redacted]
Objectives:	**Primary Objective** **Phase 1b** • To evaluate the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) and to select the recommended Phase 2 dose (RP2D) of onvansertib in combination with FOLFIRI 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** • To assess the efficacy and safety 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.
Regimen, Dose, Scheduling and Mode of Administration:	One cycle is 28 days. **Onvansertib (also known as PCM-075):** **Daily (QD) on Days 1 to 5 and 15 to 19 of a 28-day cycle:** • Phase 1b: Dose levels for the Phase 1b portion of the study ranged from 12 mg/m^2/day to 18 mg/m^2/day, orally (PO) • Phase 2: The MTD of 15 mg/m^2 onvansertib obtained from the Phase 1b portion of the study is also the RP2D and should be administered concurrently with FOLFIRI and bevacizumab **FOLFIRI (chemotherapy regimen of irinotecan, fluorouracil [5-FU], and leucovorin) + Bevacizumab:** **On Days 1 and 15 of a 28-day cycle:** • Bevacizumab 5 mg/kg, intravenous (IV) • Irinotecan 180 mg/m^2, IV • Leucovorin 400 mg/m^2, IV (required in the Phase 1b portion of the study; optional in the Phase 2 portion of the study)

	• 5-FU 400 mg/m^2, IV bolus, (required in the Phase 1b portion of the study; optional in the Phase 2 portion of the study) • 5-FU 2400 mg/m^2 continuous IV infusion for 46 hours
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. CRC patients with KRAS mutations will have histologically confirmed metastatic and unresectable disease for study eligibility. Patients must have failed treatment or be intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab. This study will consist of a Screening Period, a Treatment Period conducted in 28-day cycles, End of Treatment (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 End of Study (EOS). The starting dose and schedule of onvansertib for the Phase 1b portion of the study was selected based on analysis of pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data from a Phase 1 dose escalation study (Weiss 2018). A change in the dose and schedule of onvansertib, as well as combination with FOLFIRI and bevacizumab, may alter the toxicity of the regimen; therefore, the 12 mg/m^2/day starting dose selected for the Phase 1b portion of this study was 50% lower than the single agent RP2D dose of 24 mg/m^2/day for 5 consecutive days in a 21-day cycle that was identified in the previously completed Phase 1 study in metastatic solid tumors. Based on results from the completed Phase 1b portion of this study, the 15 mg/m^2/day, was chosen as the RP2D (and is also the MTD). The trial has been amended to enroll additional patients at 15 mg/m^2 to obtain additional PK, PD, safety, and efficacy data for this dose and schedule of onvansertib given in combination with FOLFIRI + bevacizumab. Preliminary food effect data will also be obtained under the amended protocol. Patients 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. 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. <u>Screening Period</u> Within 28 days prior to the first onvansertib dose, Screening assessments will be performed, as outlined in the Schedule of Assessments (Table 6-1). Key assessments at Screening include medical history (including a thorough review and recording of significant past medical and surgical history, current medical conditions, concomitant therapies, and TNM stage [tumor, lymph nodes, metastasis] at diagnosis), prior anti-cancer therapies, and baseline radiographic scans. Documentation of a KRAS mutation in exon 2, 3, or 4 as determined by an assay performed in a CLIA-certified laboratory must be provided for inclusion in the study. In addition, tumor tissue (archival samples or samples obtained by biopsy during the screening visit) must be

available for submission to a central laboratory for patients to be eligible for the study.

Treatment Period - Completed Phase 1b Portion of the Study

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 received one of the onvansertib dose levels shown in Synopsis Table 1. Patients also received FOLFIRI and bevacizumab as outlined in Synopsis Table 2. The starting dose level of onvansertib in the Phase 1b segment 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.

Synopsis 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.

Synopsis Table 2: Doses 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 modifications including elimination of the 5-FU bolus infusion were allowed.

The following dose escalation rules were applied to Cycle 1 of therapy in Phase 1b (the definition of DLT is provided in Section 7.1.4):

- 3 patients were initially enrolled at the first dose level.
- If 0 DLTs were observed in a 3-patient cohort at a given dose level, the dose was escalated to the next higher level.
- If exactly 1 DLT was observed in a 3-patient cohort at a given dose level, 3 additional patients were enrolled at the same dose level.
- If 2 or more DLTs were observed in a 3-patient or 6-patient cohort at a given dose level, the MTD was deemed to have been exceeded, dose escalation was stopped, and up to 3 additional patients were enrolled at the next lower dose.
- Enrollment in the Phase 1b portion of the study was completed when 6 patients had been treated at the highest possible dose level at which 1 or fewer patients experienced a DLT.

Once a dose level of onvansertib had cleared the DLT safety window, patients continuing on treatment were allowed to have their dose increased to that next higher dose level at the discretion of the Investigator. For example, if the onvansertib 15 mg/m^2 dose level was cleared for safety, patients on treatment at onvansertib 12 mg/m^2 were permitted to have their dose of onvansertib increased to 15 mg/m^2.

Treatment Period - Phase 2 Portion of the Study

The Phase 2 portion of the study commenced once the MTD/RP2D had been selected. The RP2D is 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 7.1.4). 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 selected as the RP2D (and is also the MTD). The RP2D and dose modifications for onvansertib for the Phase 2 portion of the study are shown in Synopsis Table 3. Patients will also receive FOLFIRI and bevacizumab in the Phase 2 portion of the study as shown in Synopsis Table 4.

Synopsis 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: QD=daily; RP2D=recommended Phase 2 dose.
Note: no dose reductions lower than 6 mg/m^2 are allowed, if needed the patient should be discontinued from study treatment.

Synopsis Table 4: Doses 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 Administration optional based on institutional guidelines and Investigator discretion	Days 1 and 15 of each 28-day cycle
5-FU (bolus)	One dose of 400 mg/m^2 Administration optional based on institutional guidelines and Investigator discretion	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] 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.

For those patients enrolled in the Phase 2 portion of the study who receive the optional (based on Investigator discretion) 5-FU bolus and leucovorin, occurrence of a Grade ≥ 2 neutropenia or neutropenic fever that is determined to be caused or exacerbated by the administration of the 5-FU bolus and/or leucovorin may have the 5-FU bolus and/or leucovorin eliminated in subsequent cycles, at the Investigator's discretion. If individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as

	a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2; additional details are provided in the relevant package insert(s) (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information). 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 (Table 6-1). Patients who are taken off onvansertib but remain on FOLFIRI + bevacizumab or any component(s) of the FOLFIRI + bevacizumab regimen (including 5-FU + bevacizumab "maintenance") 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. <u>End of Treatment</u> EOT evaluations should occur within 28 days (± 5 days) of the last administered dose of onvansertib. <u>Follow-Up and End of Study (EOS)</u> Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival 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 anti-cancer 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).
Sample Size:	Approximately 100 patients (18 in Phase 1b and approximately 80 patients in Phase 2)
Endpoints:	**<u>Phase 1b</u>** Characterization of 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.

	Phase 2 Primary Objective response rate (ORR) by 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 (treated-patient population). Secondary The following secondary endpoints will be explored. All efficacy evaluations will be conducted in the treated-patient population: • 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 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 assessment of food effect
Indication:	Histologically Confirmed Metastatic and Unresectable Colorectal Cancer in Patients with a KRAS Mutation
Diagnosis and Eligibility Criteria:	Patients who meet all of the following Inclusion Criteria and none of the Exclusion Criteria will be eligible to be enrolled in the study. **Inclusion Criteria:** 1. Histologically confirmed metastatic and unresectable CRC. 2. Documentation of a KRAS mutation in exon 2, 3, or 4 in primary tumor or metastasis, assessed by a CLIA-certified laboratory. Patients with concomitant KRAS and BRAF-V600 mutations are excluded from this study. Patients with Microsatellite Instability High/Deficient Mismatch Repair (MSI-H/dMMR) are also ineligible for enrollment in this study. 3. FFPE tumor tissue must be available for submission to a central laboratory in order for a patient to be eligible. If no archival tissue biopsy is available the patient must have a biopsy obtained at screening. Refer to Section 6.2.4 for guidelines regarding provision of tumor tissue samples.

	4. Age ≥ 18 years. 5. ECOG performance status of 0 or 1. 6. Signed informed consent for participation in the study. 7. Subject is not receiving any other standard-of-care or experimental cancer therapy. Patients participating in non-interventional surveys or observational studies are allowed. 8. Has failed treatment or is intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab. a. Patients must have had systemic anti-cancer therapy within 180 days of the screening visit, but can have no anti-cancer therapy within 28 days of the planned first day of treatment on study. b. Patients must have received oxaliplatin based chemotherapy with or without bevacizumab (≥ 6 weeks in duration). Patients who received maintenance therapy with fluoropyrimidines are eligible with or without rechallenge with oxaliplatin in combination with fluoropyrimidines. c. Patients who received oxaliplatin/fluoropyrimidine-based neoadjuvant or adjuvant therapy and have disease recurrence or progression > 6 months from their last dose of neoadjuvant or adjuvant treatment (or > 6 months from surgery if no adjuvant therapy was administered) will be required to have received fluoropyrimidine/oxaliplatin-based therapy with or without bevacizumab as first-line treatment for metastatic disease. d. Patients must have not received prior irinotecan. e. For patients with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen for advanced disease. f. Patients who discontinued first-line therapy because of toxicity are eligible as long as progression occurred < 6 months after the last dose of first-line therapy. 9. FOLFIRI therapy is appropriate for the patient as determined by the Investigator. 10. For a woman of child-bearing potential (WOCBP) or a male with a female partner who is a WOCBP: Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days of the final dose of any study drug. a. Adequate contraception is defined as follows: I. Complete true abstinence. II. Consistent and correct use of 1 of the following methods of birth control: i. Male partner who is sterile prior to the female patient's entry into the study and is the sole sexual partner for that female patient. ii. Implants of levonorgesterol.

iii. Injectable progestogen.
iv. Intrauterine device (IUD) with a documented failure rate of less than 1% per year.
v. Oral contraceptive pill (either combined or progesterone only).
vi. Barrier method, for example: diaphragm with spermicide or condom with spermicide in combination with either implants of levonorgesterol or injectable progestogen.

11. WOCBP must have a negative serum or urine pregnancy test within 5 days prior to enrollment.
    a. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months); or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an IUD or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child-bearing potential.
12. Imaging CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 28 days prior to the initial dose of study drug (onvansertib). Only patients with measurable disease as defined per RECIST v1.1 are eligible for enrollment. CT is the preferred imaging modality, but MRI is also accepted.
13. Must have acceptable organ function as detailed in Synopsis Table 5.

Synopsis Table 5: Acceptable Organ Function

ALT	≤ 3 institutional upper limit of normal (ULN) OR ≤ 5 ULN in presence of liver metastases
Bilirubin	≤ 1.5 ULN OR ≤ 2.0 mg/dL in presence of liver metastases
Creatinine	≤ 1.5 ULN or creatinine clearance > 50 ml/minute as calculated by the Cockcroft-Gault equation
Hgb	≥ 9.0 g/dL
ANC	≥ 1.5×10^9/L
PLTs	≥ 100×10^9/L

Abbreviations: ANC=absolute neutrophil count; Hgb=hemoglobin; PLTs=platelets; ULN=upper limit of normal.

14. Signed informed consent to provide blood sample(s) for specific correlative assays.

Exclusion Criteria:

Patients eligible for this study must not meet any of the following criteria:

	1. Concomitant KRAS and BRAF-V600 mutations or MSI-H/dMMR. 2. Anti-cancer chemotherapy or biologic therapy administered within 28 days prior to the first dose of study drug. The exception is a single dose of radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 14 days before randomization. 3. More than one prior chemotherapy regimen administered in the metastatic setting. 4. Major surgery within 6 weeks prior to enrollment. 5. Untreated or symptomatic brain metastasis. 6. Women who are pregnant or breastfeeding. 7. Gastrointestinal (GI) disorder(s) that, in the opinion of the Investigator, would significantly impede the absorption of an oral agent (e.g., intestinal occlusion, active Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection). 8. Unable or unwilling to swallow study drug. 9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure (CHF) Class II or higher according to the New York Heart Association (NYHA) Functional Classification, unstable angina pectoris, clinically significant cardiac arrhythmia (see bevacizumab cardiac exclusions below), significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements. a. Known active infection with Human Immunodeficiency Virus (HIV), with measurable viral titer, and/or active infection with hepatitis B or C (patients who have had a hepatitis B virus [HBV] immunization are eligible). b. Known active infection with SARS-CoV2 c. Clinically significant ascites or pleural effusions. 10. Known hypersensitivity to 5-FU/leucovorin. 11. Known hypersensitivity to irinotecan. 12. Abnormal glucuronidation of bilirubin; known Gilbert's syndrome. 13. Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix or prostate, or other solid tumors curatively treated with no evidence of disease for >2 years. 14. Any active disease condition that would render the protocol treatment dangerous or impair the ability of the patient to receive study drug. 15. Any condition (e.g., psychological, geographical, etc.) that does not permit compliance with the protocol. 16. Treatment with any of the drugs listed in Section 5.6 at the time of study treatment initiation.

	17. QT interval with Fridericia's correction (QTcF) > 470 milliseconds (Vandenberk 2016). The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation that are readily corrected (e.g., medications, hypokalemia), the triplicate ECG may be repeated once during Screening and that result may be used to determine eligibility. 18. Planned concomitant use of medications known to prolong the QT/QTc interval according to institutional guidelines. 19. Presence of risk factors for torsade de pointes, including family history of Long QT Syndrome or uncorrected hypokalemia. 20. The following are exclusion criteria for bevacizumab: a. History of cardiac disease: CHF Class II or higher according to the NYHA; active coronary artery disease, myocardial infarction within 6 months prior to study entry; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy, with the exception of patients who have been receiving therapy and are deemed by the Investigator to have stable/controlled disease. b. Current uncontrolled hypertension (systolic blood pressure [BP] >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management) and prior history of hypertensive crisis or hypertensive encephalopathy. c. History of arterial thrombotic or embolic events (within 6 months prior to study entry). d. Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease). e. Evidence of bleeding diathesis or clinically significant coagulopathy f. Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the study, and minor surgical procedure (excluding placement of a vascular access device) within 7 days prior to study enrollment. g. Proteinuria at Screening as demonstrated by urinalysis with proteinuria ≥2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤1g of protein in 24 hours to be eligible). h. Abdominal fistula, GI perforation, peptic ulcer, or intra-abdominal abscess within the past 6 months. i. Ongoing serious, non-healing wound, ulcer, or bone fracture. j. Known hypersensitivity to any component of bevacizumab. k. History of reversible posterior leukoencephalopathy syndrome (RPLS). 21. Use of strong CYP3A4 or UGT1A1 inhibitors or strong CYP3A4 inducers according to institutional guidelines. Patients currently

	receiving these agents who are able to switch to alternate therapy are not excluded. Inhibitors should be stopped at least 1 week prior to the first dose of protocol therapy and inducers should be stopped at least 2 weeks prior to initiation of protocol therapy.
Efficacy Evaluation:	All patients in the treated population, defined as receiving at least 1 cycle (28 days/4 weeks) of treatment, will be assessed for disease response. Radiographic imaging will be obtained during screening, prior to the start of Cycle 3 and at 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 (Table 6-1). Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival for 1 year after EOT, at which point they will be considered to have completed the study (EOS).
Safety Evaluation:	Toxicity will be graded using the NCI-CTCAE version 5.0 (Appendix 16.1). Additional safety assessments will include physical examination, medical history, ECOG performance status, weight, vital signs measurements, ECGs, and clinical laboratory testing.
Pharmacokinetic, Pharmacodynamic and Diagnostic Biomarker Evaluation and Preliminary Food Effect Study:	Tumor tissue and blood samples for pharmacokinetic and pharmacodynamic analysis and genomic profiling will be collected at pre-defined time points pre- and post-administration of onvansertib and FOLFIRI and bevacizumab and while fed or fasted as outlined in the Schedule of Assessments (Table 6-1) and Schedule of Assessments for PK sampling (Table 6-2).
Statistical Methods:	**Safety Analysis** Data for all patients who receive at least 1 dose of any study drug will be included in the safety analysis. Safety will be assessed primarily based on AEs. Other safety assessments will include data from concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, ECG measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (e.g., mean, median, range, and standard deviation for continuous data; and frequency for categorical data). **Efficacy Analysis** Patients treated in the Phase 2 portion of the study who receive at least 1 cycle of onvansertib in combination with FOLFIRI + bevacizumab will be included in the treated-patient population for efficacy analysis (Table 6-1). Patients who have radiographically-confirmed PD prior to the completion of the first cycle will be excluded from this analysis. Descriptive statistics of the ORR and the 2-sided confidence interval will be presented. Discrete endpoints will be summarized similarly. DOR, PFS and OS will be estimated using Kaplan-Meier method and summarized by median and quartiles, along with their 95% confidence intervals.

	Pharmacokinetic Analysis Summary statistics of PK parameters will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided. Log-transformation of exposure measurements may be conducted as needed. **Food Effect** To evaluate the impact of concomitant food intake, descriptive statistics of PK parameters, by fed and fasted state, along with the ratio of geometric means between fed and fasted states will be provided. Summary statistics related to this examination will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided. Log-transformation of exposure measurements may be conducted as needed for PK and pharmacodynamic associated analyses. **Pharmacodynamic Analysis** 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 pharmacodynamic analysis will include assessments of pharmacodynamic 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 pharmacodynamic analyses may be conducted as appropriate.
Sample Size Rationale	**Phase 1:** A standard 3 + 3 dose-escalation design was used in the completed Phase 1b portion of the study (Le Tourneau 2012) as described in Section 3.1.2. The dose escalation scheme and DLT evaluation plan is outlined in Section 3.1.2.1. **Phase 2:** In the Phase 2 portion of the study, patients will be enrolled and treated at the RP2D as determined in the Phase 1b portion of the study. The RP2D is 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 7.1.4). Selection of 15 mg/m^2 as the RP2D (which is also the MTD) 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. The sample size of the Phase 2 portion of the study has been increased from

	26 patients to approximately 80 patients in order to further evaluate the safety, efficacy, PK, and pharmacodynamics of the onvansertib 15 mg/m^2 dose. The group of 6 patients who were enrolled at 15 mg/m^2 in the Phase 1b portion of the study will not be included in the primary analytic cohort for the Phase 2 portion of the study but will be included 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%.

LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	Fluorouracil
ACC	Adrenocortical carcinoma
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BP	Blood pressure
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment

Abbreviation	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FLT3	Fms-like tyrosine kinase 3
FOLFIRI	Chemotherapy regimen of irinotecan, fluorouracil [5-FU], and leucovorin
FOLFOX	Treatment that is often associated with treatment of colorectal cancer; drugs involved: 5-flourouracil, leucovorin, oxaliplatin.
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
H&E	Hematoxylin and eosin
HBV	Hepatitis B virus
HDAC	Histone deacetylase
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
HTD	Highest treatment dose
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
IUD	Intrauterine device
KRAS	Kirsten rat sarcoma virus gene
M	Mitotic phase
MAF	Mutant allelic frequency
mCRPC	Metastatic castration-resistant prostate cancer

Abbreviation	Definition
MRI	Magnetic resonance imaging
MSI-H/dMMR	Microsatellite Instability High/Deficient Mismatch Repair
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease or disease progression
PFS	Progression-free survival
PI	Package insert
PK	Pharmacokinetic(s)
PLK1	Polo-like kinase 1
PLTs	Platelets
PO	Orally
PR	Partial response
QD	Daily
QTcF	QT interval with Fridericia's correction
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RP2D	Recommended Phase 2 dose
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SC	Subcutaneous
SCLC	Small cell lung cancer
SD	Stable disease
SEM	Standard error of the mean
TNBC	Triple negative breast cancer
TNM	Tumor, lymph nodes, metastasis
ULN	Upper limit of normal

Abbreviation	Definition
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

STUDY ADMINISTRATIVE STRUCTURE

Investigator:	[redacted]
Contract Research Organization:	[redacted]
Medical Monitor:	[redacted]

1 BACKGROUND

1.1 Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer mortality in US. Cancer specific mortality of CRC is predominantly due to metastatic disease. Despite significant progress in the treatment of metastatic CRC, the majority of patients with metastatic disease succumb to the disease. Therefore, improving the treatment options and effectiveness is critical in changing the outcomes for this patient population.

The Kirsten rat sarcoma virus (KRAS) gene is commonly mutated in the CRC population with more than 50% of CRC patients carrying a KRAS mutation (Cremolini 2015). In the United States (US), FOLFOX (flourouracil [5-FU], leucovorin, oxaliplatin) and FOLFIRI (5-FU, leucovorin, irinotecan) are standard-of-care options for patients with metastatic CRC in the first-line setting, irrespective of the KRAS mutation status (Abrams 2014). The majority of CRC patients respond to first-line therapy with a response rate of > 50%. Patients who respond have better survival than non-responders (Bennouna 2013). The efficacy of second-line therapy in terms of survival prolongation and response remains very limited, particularly in the KRAS-mutated population, where treatment options are more restricted. FOLFIRI (a chemotherapy regimen of irinotecan, 5-FU, and leucovorin) + bevacizumab in the second-line setting is the standard treatment in US. The response rate in the second-line setting is less than 5% as reported in a large international study of bevacizumab in the second-line setting (Tabernero 2014). However, the response rate to other antiangiogenic therapies combined with FOLFIRI in the second-line setting is 12 to 13% (Tabernero 2015, Wolf 1997).

Treatment of CRC in the KRAS-mutated population had been hampered by failure of direct targeting of KRAS (Weichert 2005). Current efforts are centered around collateral cellular pathways using combination of targeted agents and immunotherapy. Although an agent specifically targeting mutated KRAS has been approved for the treatment of cancer, this agent (sotorasib, Lumakras) is approved only for the treatment of non-small cell lung cancer (NSCLC) harboring a single specific KRAS mutation (G12C). In clinical trials, the activity of sotorasib in G12C-mutated CRC was substantially lower than that of G12C-mutated NSCLC: ORR of 7.1% and 32.2%, respectively, in a Phase 1 study of sotorasib in patients with solid tumors with the KRAS G12C mutation (Hong 2020). Thus, additional treatments are needed for patients with KRAS-mutated CRC.

Polo-like kinase 1 (PLK1) is the most well-characterized member of the family of serine/threonine protein kinases and strongly promotes the progression of cells through mitosis. PLK1 performs several important functions throughout the mitotic (M) phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome inhibitors, and the regulation of mitotic exit and cytokinesis (Degenhardt 2010).

PLK1 is ubiquitously expressed in normal proliferating tissues and is over-expressed in a wide variety of human tumors (including lung, colon, prostate, ovary, breast, and head and neck squamous cell carcinoma). The over-expression of PLK1 correlates with poor prognosis (Weichert 2004a, Weichert 2004b, Knecht 1999, Luo 2009, Wang 2016, Le Tourneau 2012).

PLK1 inhibition results in impairment of viability of several RAS mutated cell lines including HCT 116 (Luo 2009). In preclinical models, inhibition of PLK1 affects the growth of KRAS-mutated cell lines and xenografts (Wang 2016). These data make PLK1 an appealing target in KRAS mutated colorectal cancer where treatment options in the second-line setting are limited.

1.2 Onvansertib

Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1-specific adenosine triphosphate competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models (Fizazi 2017; de Bono 2017; Chi 2017; Tannock 2004; Petrylak 2004). The compound shows high potency in proliferation assays and has low nanomolar activity against a large number of cell lines from both solid and hematologic tumors. Onvansertib causes a potent mitotic cell-cycle arrest, followed by apoptosis in cancer cell lines, and inhibits xenograft tumor growth with a clear PLK1-related mechanism of action at well-tolerated doses in mice after oral administration. Onvansertib has favorable pharmacologic parameters and good oral bioavailability in rodent and nonrodent species. In addition, onvansertib has proven antitumor activity in different nonclinical models using a variety of dosing regimens, which may potentially provide flexibility in dosing schedules, and therefore, warrants investigation in clinical settings.

The major metabolic pathways found in the different animal species were N-oxidation of the N methyl-piperazine ring to give N-oxide M2 and hydroxylation on an aliphatic carbon atom of the methylene bridge of the pyrazoloquinazoline moiety to give metabolite M1. Qualitatively, no marked differences in the metabolism of onvansertib were observed between species and, quantitatively, some differences were observed cross-species.

The potential inhibitory capacity of onvansertib towards the major human cytochrome P450 (CYP) isoforms that are responsible for hepatic drug metabolism in man (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated using human liver microsomes. Onvansertib was able to inhibit the metabolic activities of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoforms to different extents, with 50% inhibitory concentration (IC_{50}) values ranging from 20 µM to 66 µM (Table 1-1). No significant inhibitory effects against CYP1A2 were detected. Considering that the concentrations relevant to achieve significant anti-tumoral activity of the compound in mice were in the order of 1 µM, the likelihood that onvansertib would show clinically relevant metabolic drug-drug interactions is considered low.

Table 1-1 Summary of Mean Inhibitor Potency of Onvansertib for Human Liver Cytochrome P450s

P450 Enzyme	Enzyme Reaction	IC_{50} (μM)[a]
CYP1A2	Tacrine 1-hydroxylation	> 100
CYP2C8	Paclitaxel 6-hydroxylation	20.2 ± 1.6
CYP2C9	Diclofenac 4-hydroxylation	20.4 ± 3.2
CYP2C19	Mephenytoin 4-hydroxylation	36.9 ± 15.7
CYP2D6	Bufuralol 1-hydroxylation	26.8 ± 5.4
CYP3A4	Testosterone 6β-hydroxylation	52.7 ± 9.8
CYP3A4	Midazolam 1'-hydroxylation	66.2 ± 4.0

Source: Report No. 0204-2007-R
Abbreviations: IC_{50}=inhibitory drug concentration that produces 50% of the maximal effect; SEM=standard error of mean.
a Data are mean ± SEM.

Onvansertib has been evaluated preclinically in combination with several different cytotoxic anti-cancer drugs, including irinotecan, cisplatin, cytarabine, doxorubicin, gemcitabine and paclitaxel, and with targeted therapeutics such as abiraterone, histone deacetylase (HDAC) inhibitors, fms-like tyrosine kinase 3 (FLT3) inhibitors, and bortezomib. These therapies are used clinically for the treatment of many hematologic and solid cancers, including acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), metastatic CRC, metastatic castration-resistant prostate cancer (mCRPC), adrenocortical carcinoma (ACC), triple negative breast cancer (TNBC), small cell lung cancer (SCLC), and ovarian cancer.

At the time of initiation of the Phase 1b portion of this study, a single Phase 1 safety study with onvansertib had been completed in adult patients with advanced/metastatic solid tumors at a single study site in the US (Weiss 2018). The primary objective was to determine first cycle dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of onvansertib administered orally as a single agent for 5 consecutive days every 3 weeks (i.e., a 21-day treatment cycle). Secondary objectives were to define the safety profile of onvansertib, to determine the pharmacokinetics (PK) of onvansertib in plasma (at the MTD), and to document any antitumor activity. A total of 21 patients were enrolled, and 19 patients were treated. No DLTs occurred at the first 3 dose levels (doses of 6, 12, and 24 mg/m^2/day). At the subsequent dose level (dose of 48 mg/m^2/day), 2 of 3 patients developed DLTs. An intermediate dose level of 36 mg/m^2/day was investigated. At the intermediate dose level, 4 patients were treated and 2 DLTs were observed. After further cohort expansion, the MTD for onvansertib given as a single agent given on 5 consecutive days of a 21-day cycle was determined to be 24 mg/m^2/day. The best observed treatment response was stable disease (SD); SD occurred in 5 of the 16 evaluable patients. The study identified thrombocytopenia and neutropenia as the most common toxicities; this is consistent with the expected mechanism of action of onvansertib and with results from the preclinical studies. These hematologic toxicities were reversible, with recovery usually occurring within 3 weeks of last dose of drug.

Three additional clinical studies of onvansertib are currently ongoing: Study TROV-053 (A Phase 2 Study of PCM-075 in Combination with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer), Study TROV-052 (A Phase 1b/2 Study of PCM-075 in Combination with either Low-Dose Cytarabine or Decitabine in Patients with AML and Study CRDF-001 (A Phase 2 clinical study of onvansertib in combination with nanoliposomal irinotecan, leucovorin, and 5-FU for the second-line treatment of patients with metastatic pancreatic ductal adenocarcinoma).

Additional details regarding the nonclinical and clinical studies of onvansertib are provided in the onvansertib Investigator's Brochure (onvansertib IB).

1.3 Rationale

PLK1 is a potential target for inhibition in KRAS-mutated CRC and may provide a new second-line treatment option for patients with mCRC harboring a KRAS mutation. This Phase 1b/2 study is proposed to assess the tolerated dose, safety, and efficacy of onvansertib in combination with FOLFIRI + bevacizumab in patients with KRAS-mutated histologically confirmed metastatic and unresectable CRC in the second-line setting.

1.4 Dose Rationale

The starting dose and schedule of onvansertib for the Phase 1b portion of this study was selected based on analysis of pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data from the initial Phase 1 dose escalation study (Weiss 2018). A change in the dose and schedule of onvansertib, as well as combination with FOLFIRI and bevacizumab, may alter the toxicity of the regimen; therefore, the starting dose selected for the Phase 1b portion of this study was 12 mg/m^2/day. The 12 mg/m^2/day starting dose was 50% lower than the single-agent recommended Phase 2 dose (RP2D) dose of 24 mg/m^2/day for 5 consecutive days in a 21-day cycle that was identified in the previously completed Phase 1 study in metastatic solid tumors (Weiss 2018).

2 STUDY DESIGN OBJECTIVES AND ENDPOINTS

This is a multicenter, open-label, single-arm study of the safety and efficacy of onvansertib in combination with FOLFIRI and bevacizumab.

2.1 Objectives

2.1.1 Phase 1b

To evaluate the DLTs and MTD and to select the recommended Phase 2 dose (RP2D) 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.

2.1.2 Phase 2

To assess the efficacy and safety 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.

2.2 Endpoints

2.2.1 Endpoints for the Completed Phase 1b Portion of the Study

The primary endpoint of the completed Phase 1b portion of the study was characterization of DLTs; characterization of adverse events (AEs) by type, incidence, severity (graded by National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] version 5.0; Appendix 16.1), 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 (Appendix 16.2).

2.2.2 Endpoints for the Phase 2 Portion of the Study

Primary

The primary endpoint of Phase 2 is the objective response rate (ORR) by 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 (treated-patient population).

Secondary

The following secondary endpoints will be explored. All efficacy evaluations will be conducted in the treated-patient population:

- 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 the 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

Exploratory

- Use of circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA) to evaluate relevant biomarkers correlated with patient response
- Use of formalin-fixed, paraffin-embedded (FFPE) tumor tissue to evaluate baseline genomic profiles (DNA/RNA) associated with patient response
- Preliminary assessment of food effect

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, open-label, single-arm study of the safety and efficacy of onvansertib in combination with FOLFIRI and bevacizumab.

This study will consist of a Screening Period, a Treatment Period conducted in 28-day cycles, End of Treatment (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 study (EOS).

Patients will continue treatment in the 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. 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.

A subgroup of patients (at least 12 patients) enrolled in the Phase 2 portion of the study will participate in a preliminary food effect study. See Section 6.2.11.4 for more details.

3.1.1 Screening Period

Within 28 days prior to the first onvansertib dose, Screening assessments will be performed, as outlined in the Schedule of Assessments (Table 6-1). Study procedures are outlined in detail in Section 6. In the Phase 2 segment of the study, under protocol version 2.0, FFPE tumor tissue must be available for submission. If archival tissue is not available, patients must undergo a biopsy at screening to obtain tissue for eligibility.

3.1.2 Treatment Period for the Completed Phase 1b Portion of the Study

A standard 3 + 3 dose-escalation design was used (Le Tourneau 2012). Patients were enrolled to receive one of the onvansertib dose levels shown in Table 5-1, and also to receive FOLFIRI and bevacizumab as outlined in Table 5-3. The starting dose level of onvansertib was 12 mg/m^2/day for Days 1 to 5 and 15 to 19 of each 28-day treatment cycle. Onvansertib was administered concurrently with FOLFIRI and bevacizumab.

3.1.2.1 Dose Escalation and Dose-limiting Toxicity

The following dose escalation rules were applied to Cycle 1 of therapy in Phase 1b (the definition of DLT is provided in Section 7.1.4):

- 3 patients were initially enrolled at the first dose level.
- If 0 DLTs were observed in a 3-patient cohort at a given dose level, the dose was escalated to the next higher level.
- If exactly 1 DLT was observed in a 3-patient cohort at a given dose level, 3 additional patients were enrolled at the same dose level.

- If 2 or more DLTs were observed in a 3-patient or 6-patient cohort at a given dose level, the MTD was deemed to have been exceeded, dose escalation was stopped, and up to 3 additional patients were enrolled at the next lower dose.
- Enrollment in the Phase 1b portion of the study was completed when 6 patients had been treated at the highest dose level at which 1 or fewer patients experienced a DLT.

Once a dose level of onvansertib had cleared the DLT safety window, patients continuing on treatment were allowed to have their dose increased to that next higher dose level at the discretion of the Investigator. For example, if the onvansertib 15 mg/m^2 dose level had been cleared for safety, patients on treatment at onvansertib 12 mg/m^2 were permitted to have their dose of onvansertib increased to 15 mg/m^2.

3.1.3 Treatment Period for the Phase 2 Portion of the Study

Phase 2 commenced once 15 mg/m^2 was selected as the RP2D (is also the MTD). The sample size of the Phase 2 portion of the study has been increased from 26 patients to approximately 80 patients in order to further evaluate the safety and efficacy of the onvansertib 15 mg/m^2 dose.

3.1.3.1 Recommended Phase 2 Dose

The RP2D is 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 7.1.4). 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 selected as the RP2D (and is also the MTD).

3.1.3.2 Dose Modification Guidelines

For those patients enrolled in the Phase 2 portion of the study who receive the optional (at Investigator's discretion) 5-FU bolus and leucovorin, occurrence of a Grade $\geq$ 2 neutropenia or neutropenic fever that is determined to be caused or exacerbated by the administration of the 5-FU bolus and/or leucovorin may have the 5-FU bolus and/or leucovorin eliminated in subsequent cycles, at the Investigator's discretion. If individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios.

Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2; additional details are provided in the relevant package insert(s) (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information).

3.1.4 End of Treatment

The EOT visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1). The EOT visit is described further in Section 6.2.13.

3.1.5 Follow-up and End of Study

Patients (any ongoing from Phase 1b and those from Phase 2) will be followed for overall survival 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 anti-cancer 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).

3.2 Study Duration

The Screening Period will be up to 28 days prior to the first dose of onvansertib. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until PD or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival 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 anti-cancer 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).

4 STUDY POPULATION

4.1 Eligibility Criteria

Patients who meet all of the following Inclusion Criteria and none of the Exclusion Criteria will be eligible to be enrolled in the study.

4.1.1 Inclusion Criteria

1. Histologically confirmed metastatic and unresectable CRC.
2. Documentation of a KRAS mutation in exon 2, 3, or 4 in primary tumor or metastasis, assessed by a CLIA-certified laboratory. Patients with concomitant KRAS and BRAF-V600 mutations are excluded from this study. Patients with Microsatellite Instability High/Deficient Mismatch Repair (MSI-H/dMMR) are also ineligible for enrollment in this study.
3. FFPE tumor tissue must be available for submission to a central laboratory in order for a patient to be eligible. If no archival tissue biopsy is available the patient must have a biopsy obtained at screening. Refer to Section 6.2.4 for guidelines regarding provision of tumor tissue samples.
4. Age ≥ 18 years.
5. ECOG performance status of 0 or 1 (Appendix 16.2).
6. Signed informed consent for participation in the study.
7. Subject is not receiving any other standard-of-care or experimental cancer therapy. Patients participating in non-interventional surveys or observational studies are allowed.
8. Has failed treatment or is intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab.
    a. Patients must have had systemic therapy within 180 days of the screening visit, but can have no anti-cancer therapy within 28 days of the planned first day of treatment on study.
    b. Patients must have received oxaliplatin based chemotherapy with or without bevacizumab (≥ 6 weeks in duration). Patients who received maintenance therapy with fluoropyrimidines are eligible with or without rechallenge with oxaliplatin in combination with fluoropyrimidines.
    c. Patients who received oxaliplatin/fluoropyrimidine-based neoadjuvant or adjuvant therapy and have disease recurrence or progression > 6 months from their last dose of neoadjuvant or adjuvant treatment (or > 6 months from surgery if no adjuvant therapy was administered) will be required to have received fluoropyrimidine/oxaliplatin-based therapy with or without bevacizumab as first-line treatment for metastatic disease.
    d. Patients must not have received prior irinotecan.
    e. For patients with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen for advanced disease.
    f. Patients who discontinued first-line therapy because of toxicity are eligible as long as progression occurred < 6 months after the last dose of first-line therapy.

9. FOLFIRI therapy is appropriate for the patient as determined by the Investigator.
10. For a woman of child-bearing potential (WOCBP) or a male with a female partner who is a WOCBP: Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days of the final dose of any study drug.
    a. Adequate contraception is defined as follows:
        I. Complete true abstinence.
        II. Consistent and correct use of 1 of the following methods of birth control:
            i. Male partner who is sterile prior to the female patient's entry into the study and is the sole sexual partner for that female patient.
            ii. Implants of levonorgesterol.
            iii. Injectable progestogen.
            iv. Intrauterine device (IUD) with a documented failure rate of less than 1% per year.
            v. Oral contraceptive pill (either combined or progesterone only).
            vi. Barrier method, for example: diaphragm with spermicide or condom with spermicide in combination with either implants of levonorgesterol or injectable progestogen.
11. WOCBP must have a negative serum or urine pregnancy test within 5 days prior to enrollment.
    a. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months); or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an IUD or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child-bearing potential.
12. Imaging computed tomography (CT)/magnetic resonance imaging (MRI) of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 28 days prior to the first dose of onvansertib. Only patients with measurable disease as defined per RECIST v1.1 are eligible for enrollment. CT is the preferred imaging modality, but MRI is also accepted.
13. Must have acceptable organ function as detailed in Table 4-1:

Table 4-1 Acceptable Organ Function

ALT	≤ 3 institutional ULN OR ≤ 5 ULN in presence of liver metastases
Bilirubin	≤ 1.5 ULN OR ≤ 2.0 mg/dL in presence of liver metastases
Creatinine	≤ 1.5 ULN OR creatinine clearance > 50 ml/min as calculated by the Cockcroft-Gault equation
Hgb	≥ 9.0 g/dL

ANC	≥ 1.5 × 109/L
PLTs	≥ 100 × 109/L

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; Hgb=hemoglobin; PLTs=platelets; ULN=upper limit of normal.

14. Signed informed consent to provide blood sample(s) for specific correlative assays.

4.1.2 Exclusion Criteria

Patients eligible for this study must not meet any of the following exclusion criteria:

1. Concomitant KRAS and BRAF-V600 mutation or MSI-H/dMMR.
2. Anti-cancer chemotherapy or biologic therapy administered within 28 days prior to the first dose of study drug. The exception is a single dose of radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 14 days before randomization.
3. More than one prior chemotherapy regimen administered in the metastatic setting.
4. Major surgery within 6 weeks prior to enrollment.
5. Untreated or symptomatic brain metastasis.
6. Women who are pregnant or breastfeeding.
7. Gastrointestinal (GI) disorder(s) that, in the opinion of the Investigator, would significantly impede the absorption of an oral agent (e.g., intestinal occlusion, active Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection).
8. Unable or unwilling to swallow study drug.
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure (CHF) Class II or higher according to the New York Heart Association (NYHA) Functional Classification, unstable angina pectoris, clinically significant cardiac arrhythmia (see bevacizumab cardiac exclusions below), significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.
    a. Known active infection with Human Immunodeficiency Virus (HIV), with measurable viral titer, and/or active infection with hepatitis B or C (patients who have had a hepatitis B virus (HBV) immunization are eligible).
    b. Known active infection with SARS-CoV-2
    c. Clinically significant ascites or pleural effusions.
10. Known hypersensitivity to 5-FU/leucovorin.
11. Known hypersensitivity to irinotecan.
12. Abnormal glucuronidation of bilirubin; known Gilbert's syndrome.

13. Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix or prostate, or other solid tumors curatively treated with no evidence of disease for > 2 years.
14. Any active disease condition that would render the protocol treatment dangerous or impair the ability of the patient to receive study drug.
15. Any condition (e.g., psychological, geographical, etc.) that does not permit compliance with the protocol.
16. Treatment with any of the drugs listed in Section 5.6 at the time of study treatment initiation.
17. QT interval with Fridericia's correction (QTcF) > 470 milliseconds (Vandenberk 2016). The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation that are readily corrected (e.g., medications, hypokalemia), the triplicate ECG may be repeated once during Screening and that result may be used to determine eligibility.
18. Planned concomitant use of medications known to prolong the QT/QTc interval according to institutional guidelines.
19. Presence of risk factors for torsade de pointes, including family history of Long QT Syndrome or uncorrected hypokalemia.
20. The following are exclusion criteria for bevacizumab:
    a. History of cardiac disease: CHF Class II or higher according to the NYHA; active coronary artery disease, myocardial infarction within 6 months prior to study entry; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy, with the exception of patients who have been receiving therapy and are deemed by the Investigator to have stable/controlled disease.
    b. Current uncontrolled hypertension (systolic blood pressure [BP] > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management) and prior history of hypertensive crisis or hypertensive encephalopathy.
    c. History of arterial thrombotic or embolic events (within 6 months prior to study entry).
    d. Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease).
    e. Evidence of bleeding diathesis or clinically significant coagulopathy.
    f. Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the study, and minor surgical procedure (excluding placement of a vascular access device) within 7 days prior to study enrollment.
    g. Proteinuria at Screening as demonstrated by urinalysis with proteinuria ≥ 2+ (patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).
    h. Abdominal fistula, GI perforation, peptic ulcer, or intra-abdominal abscess within the past 6 months.
    i. Ongoing serious, non-healing wound, ulcer, or bone fracture

j. Known hypersensitivity to any component of bevacizumab
k. History of reversible posterior leukoencephalopathy syndrome (RPLS)

21. Use of strong CYP3A4 or UGT1A1 inhibitors or strong CYP3A4 inducers. Patients currently receiving these agents who are able to switch to alternate therapy are not excluded. Inhibitors should be stopped at least 1 week prior to the first dose of protocol therapy and inducers should be stopped at least 2 weeks prior to initiation of protocol therapy.

4.2 Removal of Patients From Therapy or Assessment

Patients will be discontinued from study drug administration for any of the following reasons:

- Intolerable toxicity as determined by the Investigator
- Progression of disease (PD) requiring an alternate therapy, in the opinion of Investigator
- Entry into another investigational clinical study or start of additional anti-cancer therapy (participation in non-interventional surveys or observational studies are allowed)
- Significant deviation from the protocol or eligibility criteria, in the opinion of the Medical Monitor and/or Investigator
- Noncompliance with study procedures
- Patient withdrawal of consent or decision to discontinue participation
- Termination of the study by the Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study

In the event that a patient is withdrawn from treatment and/or the study, every effort will be made by the Investigator to document and report the reasons for withdrawal as completely as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient's electronic Case Report Form (eCRF). An eCRF must be completed for any patient who receives study drug. An EOT reason must be recorded for any patient who receives study drug. The requirements for patient replacement are outlined in Section 8.

If a patient is discontinued from treatment or the study for any reason, every effort must be made to perform all EOT assessments (Section 6.1). In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record, and should be reported as a deviation.

If individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios. See also Sections 3.1.3.2 and 5.3.

5 STUDY DRUG TREATMENT

5.1 Description

5.1.1 Onvansertib (PCM-075)

The chemical name of onvansertib (PCM-075H) is 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl] amino}- 4,5-dihydro-1H-pyrazolo[4,3-h] quinazoline-3-carboxamide fumarate salt.

Onvansertib will be supplied as 5 mg and 20 mg (as free base) hard gelatin capsules that will be administered orally (PO).

- A size 4 opaque caramel body and Swedish orange cap hard gelatin capsule contains 6.09 mg of onvansertib (PCM-075H) corresponding to 5 mg as free base, lactose monohydrate, pregelatinized starch, and glyceryl behenate. The capsule body shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide; the capsule cap shell contains gelatin, red iron oxide, and titanium dioxide.
- A size 4 opaque Swedish orange body and cap hard gelatin capsule contains 24.36 mg of onvansertib (PCM-075H) corresponding to 20 mg as free base, lactose monohydrate, pregelatinized starch, and glyceryl behenate. The capsule shell contains gelatin, red iron oxide, and titanium dioxide.

5.1.1.1 Storage

Onvansertib is stable at room temperature for up to 12 months. However, for optimal shelf-life, onvansertib is to be stored under refrigerated conditions (5°C ± 3°C; 36°F to 46°F) in the original packaging prior to usage. The research pharmacy may dispense onvansertib in standard pharmacy amber vials. Onvansertib does not need to be transported with ice packs, but once brought to patient's home, it should be stored in a refrigerator, ideally within 24 hours.

5.1.1.2 Shelf-life

When onvansertib is stored at 5°C ± 3°C (36°F to 46°F), on the basis of the available stability information, a shelf-life of 48 months is currently assigned to the 5 mg and 20 mg (as free base) hard gelatin capsules.

Concurrent stability studies on the clinical batches are being conducted with 5 mg and 20 mg (as free base) hard gelatin capsules in order to evaluate the chemical, physical, and microbiological parameters. The onvansertib expiry date will be extended accordingly with the stability results. Any unexpected findings will be promptly communicated to Investigators and to the applicable regulatory authorities.

5.1.2 FOLFIRI

FOLFIRI is a chemotherapy regimen made up of the following drugs:

- Folinic acid (leucovorin; refer to the Leucovorin Prescribing Information), a vitamin B derivative used as a "rescue" drug for high doses of the drug methotrexate, but increases

the cytotoxicity of 5-FU;

- Fluorouracil (5-FU; refer to the Fluorouracil Prescribing Information), a pyrimidine analog and antimetabolite that incorporates into the DNA molecule and stops synthesis; and
- Irinotecan (Camptosar; refer to Camptosar Prescribing Information), a topoisomerase inhibitor that prevents DNA from uncoiling and duplicating.

FOLFIRI will be supplied by the site according to applicable local regulatory requirements.

5.1.2.1 Storage Conditions

Packaging, labelling, and storage of FOLFIRI will be in accordance with the prescribing information (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information), and the Pharmacy Manual.

5.1.3 Bevacizumab

Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product (Avastin Prescribing Information).

Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP (Avastin Prescribing Information).

Bevacizumab will be supplied by the site according to applicable local regulatory requirements.

5.1.3.1 Storage Conditions

Packaging, labelling, and storage of bevacizumab will be in accordance with the prescribing information (Avastin Prescribing Information), and the Pharmacy Manual.

5.2 Administration

5.2.1 Onvansertib Administration

Completed Phase 1b Portion of the Study

Administration was performed in accordance with the dose cohorts/levels outlined in Table 5-1 for the completed Phase 1b portion of the study and at the time points outlined in the Schedules of Assessments (Table 6-1).

The starting dose of onvansertib was 12 mg/m^2 administered PO on Day 1 through Day 5 and Day 15 through Day 19 of each 28-day treatment cycle. Dosing of onvansertib was administered concurrently with dosing of FOLFIRI and bevacizumab.

Table 5-1 Dose Levels of Onvansertib in the Completed Phase 1b Portion of the Study

Study Phase	Dose Level	Dose	Frequency
Phase 1b	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.

Phase 2 Portion of the Study

Based on results of the Phase 1b portion of this study, 15 mg/m^2/day was selected as the RP2D (also the MTD). The RP2D and dose modifications for onvansertib for the Phase 2 portion of the study are shown in Table 5-2.

Table 5-2 Dose Modifications for Onvansertib in the Phase 2 Portion of the Study

Study Phase	Dose Level	Dose	Frequency
Phase 2	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: QD=daily; RP2D=recommended Phase 2 dose.
Note: no dose reductions lower than 6 mg/m^2 are allowed, if needed the patient should be discontinued from study treatment.

5.2.1.1 Food Restrictions

Onvansertib should be administered after an overnight fast, with free access to water. Drug should be taken with a large glass of plain water without ice. A light breakfast can be served 3 hours after drug intake.

See Section 6.2.11.4 for information on PK food effect substudy.

5.2.1.2 Dose Rounding

Dose rounding is to the nearest 5 mg, rounded up for dose calculations ending in 0.5 to 0.9. For example, at the RP2D of 15 mg/m^2 the daily dose is calculated at 27 mg and would be rounded up to 30 mg, provided as one 20 mg capsule and two 5 mg capsules of onvansertib.

5.2.2 FOLFIRI and Bevacizumab Administration

Completed Phase 1b Portion of the Study

Administration of FOLFIRI and bevacizumab for the completed Phase 1b portion of the study were in accordance with the doses outlined in Table 5-3, and at the time points outlined in the Schedule of Assessments (Table 6-1). Detailed information for the individual drugs is available in the prescribing information (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information).

Table 5-3 Doses of FOLFIRI and Bevacizumab in the Completed Phase 1b Portion of the Study

Study Phase	Drug	Dose	Frequency
Phase 1b	**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 modifications including elimination of the 5-FU bolus infusion were allowed.

Phase 2 Portion of the Study

Administration of FOLFIRI and bevacizumab for the Phase 2 portion of the study should be in accordance with the doses outlined in Table 5-4, and at the time points outlined in the Schedule of Assessments (Table 6-1). After evaluation of safety data from the Phase 1b portion of the study, the 5-FU bolus and leucovorin will be optional, at the investigator's discretion, for any patients in the Phase 2 portion of the study enrolled under version 2.0 of the protocol. All patients in the Phase 2 portion will receive the 46-hour 5-FU continuous infusion.

Detailed information for the individual drugs is available in the prescribing information (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information).

Table 5-4 Doses of FOLFIRI and Bevacizumab in the Phase 2 Portion of the Study

Study Phase	Drug	Dose	Frequency
Phase 2	**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 Administration optional based on institutional guidelines and Investigator discretion	Days 1 and 15 of each 28-day cycle
	5-FU (bolus)	One dose of 400 mg/m^2 Administration optional based on institutional guidelines and Investigator discretion	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] 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.

5.3 Dose Modifications

For those patients enrolled in the Phase 2 portion of the study (this was also applied to patients enrolled in the Phase 1b portion of the study) who receive the 5-FU bolus and leucovorin, occurrence of a Grade ≥ 2 neutropenia or neutropenic fever that is determined to be caused or exacerbated by the administration of the 5-FU bolus and/or leucovorin may have the 5-FU bolus and/or leucovorin eliminated in subsequent cycles, at the Investigator's discretion.

Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2 and will be based on dose modification guidelines provided in Table 5-6 and Table 5-7; additional details for FOLFIRI and bevacizumab are provided in the relevant package insert (PI).

As per Table 5-7, for any Grade 1 and 2 nausea or vomiting, maximize the antiemetic regimen prescribed to the patient. For Grade 3 nausea or vomiting, reduce irinotecan for the next cycle. For each subsequent cycle, the patient may continue irinotecan at the previous dose level, provided nausea has resolved to Grade 2 or 1. For Grade 4 nausea or vomiting, discontinue 5-FU bolus (if using) and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite 2 treatments with adequate (combination) antiemetic therapy.

As per Sections 3.1.3.2 and 4.2, if individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or

irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios.

5.3.1 Onvansertib Dose Modifications

5.3.1.1 Dose Delays

Patients who experience any Grade 3 or higher AE considered related to onvansertib (i.e., adverse reaction or suspected adverse reaction according to the criteria in Section 7.3) will have their next dose of onvansertib held until all study drug-related toxicities have improved to Grade 1 or to Baseline. If the AE does not resolve to Grade 1 or less or to Baseline within 2 weeks, the patient will be discontinued from treatment, unless the investigator believes it is in the patient's best interest to delay more than 2 weeks and has discussed the case and obtained approval of the Medical Monitor to restart the treatment after a delay longer than 2 weeks. In the Phase 2 portion of the trial, if a patient experiences recurrent Grade 3 or higher toxicity related to onvansertib at the lowest allowed onvansertib dose (6 mg/m^2), treatment with onvansertib must be discontinued as no further dose reductions are allowed. Dose delays do not alter the Schedule of Assessments. If pharmacokinetic or pharmacodynamic studies are scheduled at the time of a dose delay, these will be delayed, and should be rescheduled by the Investigator and Sponsor.

If treatment is delayed for 7 days, e.g., Cycle 1 Day 15 must be delayed to Day 22, then the numbering of the subsequent dose will not change, e.g., the treatment given on Day 22 will be considered the Cycle 1 Day 15 dose. However, if treatment is delayed for 14 days or greater, then the next treatment will be considered Day 1 of the subsequent cycle. Examples: if Cycle 1 Day 15 is delayed by 14 days, the next treatment will be considered the Cycle 2 Day 1 treatment. If Cycle 2 Day 1 is delayed by 14 days, the next treatment will still be considered the Cycle 2 Day 1 treatment.

If a patient forgets to take their dose of study drug on any day during Days 1 to 5 or 15 to 19 of the cycle, they will have the opportunity to take the scheduled dose within 4 to 6 hours of the original scheduled time on that same day. If a patient misses a dose of study drug on any day during Days 1 to 5 or Days 15 to 19 of the cycle, they will not be able to make up the missed dose on the next day or move the Day 1 to 5 or Day 15 to 19 dosing schedule out to additional consecutive days (e.g., Day 6, Day 20, etc.). If onvansertib is vomited, participants should not retake drug, but should take it instead at the next scheduled time.

5.3.1.2 Dose Reduction

Completed Phase 1b Portion of the Study

If a DLT resolved to Grade 1 or less, the dose of onvansertib was reduced to the next lower dose level in subsequent cycles based on Investigator discretion (see Section 5.2.1, Table 5-1).

Phase 2 Portion of the Study

Dose reduction levels for onvansertib in the Phase 2 portion of the study are outlined in Section 5.2.1, Table 5-2.

Onvansertib-related hematologic AEs require modifications to the onvansertib dose per Table 5-5:

Table 5-5 Dose Reductions for Onvansertib-Related Hematologic Toxicities

HEMATOLOGIC TOXICITIES	
Dose modifications recommended for the next treatment cycle based on toxicity experienced during a previous cycle (i.e., after Days 1-5 or 15-19 of any cycle):	
Grade 3 or 4 neutropenia or thrombocytopenia	
1st occurrence	Continue onvansertib at current dose level
2nd occurrence	Continue onvansertib at one lower dose level
Febrile neutropenia (defined as ANC < 1000/µL and T ≥ 38.5°C)	
1st occurrence	Continue onvansertib at current dose level
2nd occurrence	Continue onvansertib at one lower dose level

5.3.1.3 Dose Escalation

Completed Phase 1b Portion of the Study

In the completed Phase 1b portion of the study, once a dose level of onvansertib had cleared the DLT safety window, patients continuing on treatment were allowed to have their dose increased to that next higher dose level at the discretion of the Investigator. For example, if the onvansertib 15 mg/m^2 dose level had been cleared for safety, patients on treatment at onvansertib 12 mg/m^2 were permitted to have their dose of onvansertib increased to 15 mg/m^2.

5.3.2 FOLFIRI and Bevacizumab Dose Modifications

Should a patient experience a Grade ≥ 2 neutropenia or neutropenic fever during treatment, a dose modification will be allowed for the treatment component(s) deemed probable for the etiology of the toxicity.

Any necessary dose reductions for FOLFIRI should follow those outlined in Table 5-6, and should be in accordance with the dose modification guidelines presented in Table 5-7. Additional details for FOLFIRI and bevacizumab are provided in the relevant package insert (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information). Note: if irinotecan is discontinued due to toxicity, all other study drugs may be continued (5-FU, bevacizumab, and onvansertib).

Table 5-6 Dose Reductions of FOLFIRI

Drug	Starting Dose	Dose Reduction 1	Dose Reduction 2	Dose Reduction 3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	90 mg/m^2
Leucovorin[a]	400 mg/m^2; administration optional based on Investigator discretion	Investigator discretion	Investigator discretion	Investigator discretion
5-FU (bolus)[b]	400 mg/m^2	Discontinue	Discontinue	Discontinue
5-FU (infusion)[b]	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2	1200 mg/m^2

Abbreviations: 5-FU=fluorouracil.

[a] In the completed Phase 1b portion of the study, patients received leucovorin as a 400 mg/m^2 bolus. In the Phase 2 portion of the study, the dosing of leucovorin is at the discretion of the Investigator. 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.

[b] In the completed Phase 1b portion of the study, patients received 5-FU as a 400 mg/m^2 bolus with allowed modifications based on toxicity. In the Phase 2 portion of the study, the use of the 5-FU bolus is at the discretion of the Investigator.

Table 5-7 Dose Modification Guidelines for FOLFIRI and Bevacizumab

Dose Modification Guidelines for FOLFIRI and Bevacizumab	
HEMATOLOGIC TOXICITIES	
Dose modifications recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 or 15 of any cycle):	
Grade 2 neutropenia or thrombocytopenia	
	Discontinue 5-FU bolus and continue all other agents at the current dose level
Grade 3 or 4 neutropenia or thrombocytopenia	
	Suspend chemotherapy (FOLFIRI and bevacizumab) and onvansertib
	If counts recover to ANC ≥ 1000/μL and platelets ≥ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows:
	Discontinue 5-FU bolus
	Continue 5-FU infusion and irinotecan at one lower dose level
Febrile neutropenia (defined as ANC < 1000/μL and T ≥ 38.5°C)	
	Suspend chemotherapy (FOLFIRI and bevacizumab) and onvansertib
	If fever resolves, and counts recover to ANC ≥ 1000/μL and platelets ≥ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows:
	Discontinue 5-FU bolus

Dose Modification Guidelines for FOLFIRI and Bevacizumab	
	Continue 5-FU infusion and irinotecan at one lower dose level
GASTROINTESTINAL TOXICITIES	
GI PERFORATION OR INTRA-ABDOMINAL FISTULA	
	Discontinue bevacizumab
DIARRHEA	
Early cholinergic syndrome may occur during or shortly after receiving irinotecan	
	It is strongly suggested that Atropine, 0.25 – 1.0 mg IV or subcutaneous (SC) be used at the time of irinotecan administration to prevent these symptoms. Additional antidiarrheal measures may be used at the discretion of the Investigator.
Late diarrhea (e.g., developing more than 24 hours after irinotecan)	
	Manage with loperamide. For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, patients will be instructed to begin taking loperamide. Additional antidiarrheal measures may be used at the discretion of the Investigator. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.
Concomitant medications and/or dose modifications based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):	
	Oral fluoroquinolone treatment should be initiated for any of the following events:
	Diarrhea persisting for more than 24 hours despite loperamide
	ANC < 500/μL (even in the absence of diarrhea or fever)
	Fever with diarrhea (even in the absence of neutropenia)
	Antibiotic therapy should also be initiated in patients who are hospitalized with prolonged diarrhea (even in the absence of neutropenia)
Grade 2 diarrhea	
	Discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next dose. For each subsequent dose, resume 5-FU infusion and irinotecan at the previous dose levels, provided diarrhea has fully resolved.
Grade 3 or 4 diarrhea	
	Suspend all protocol therapy. If diarrhea resolves to ≤ Grade 2 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.

Dose Modification Guidelines for FOLFIRI and Bevacizumab	
MUCOSITIS	
Dose modifications based on the grade of mucositis seen on the day of treatment for any day after Day 1 in any cycle:	
Grade 2 mucositis	
	May discontinue 5-FU bolus (if using). Reduce 5-FU infusion and irinotecan one dose level for the next dose. For each subsequent cycle, may resume 5-FU infusion and irinotecan at the previous dose levels, provided mucositis has fully resolved.
Grade 3 or 4 mucositis	
	Suspend all protocol therapy.
	If mucositis resolves to ≤ Grade 2 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.
NAUSEA/VOMITING	
Dose modifications based on the grade of nausea and vomiting occurring during a cycle (i.e., after Day 1 in any cycle):	
Grade 1 and 2 nausea or vomiting	
	Maximize the antiemetic regimen prescribed to the patient
Grade 3 nausea or vomiting	
	Reduce irinotecan one dose level for the next dose
	For each subsequent cycle, may continue irinotecan at previous dose level, provided nausea has resolved ≤ Grade 2.
Grade 4 nausea or vomiting	
	Discontinue 5-FU bolus (if using) and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite 2 treatments with adequate (combination) antiemetic therapy.
HYPERTENSION	
	Maintain the majority of blood pressures < 150/90 mmHg with the use of antihypertensive medications, dose delays and discontinuation of bevacizumab. The Investigator should use best medical practice in treating hypertension.
THROMBOTIC EVENTS	
Patients should be carefully monitored for evidence of thromboembolic disease during treatment.	
VENOUS THROMBOTIC EVENTS	
Grade 3 venous thrombosis or asymptomatic pulmonary embolism	
	Skip bevacizumab. Resume bevacizumab once the patient on stable dose of anticoagulation without any evidence of bleeding.

Dose Modification Guidelines for FOLFIRI and Bevacizumab	
Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of bevacizumab	
	Discontinue all protocol therapy.
Symptomatic pulmonary embolism	
	Discontinue all protocol therapy.
ARTERIAL THROMBOTIC EVENTS	
Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy	
	Discontinue bevacizumab. Patients may continue other protocol therapy.
Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia	
	Discontinue bevacizumab. Patients may continue other protocol therapy.
Grade 3 cardiac ischemia/infarction	
	Discontinue all protocol therapy.
Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia	
	Discontinue all protocol therapy.
HEMORRHAGE/BLEEDING	
Grade 3 hemorrhage/bleeding	
	Discontinue bevacizumab and skip other protocol therapy; once hemorrhage or bleeding resolves, other protocol therapy may be continued at the treating physician's discretion.
Grade 4 hemorrhage/bleeding	
	Discontinue all protocol therapy.
PROTEINURIA	
2+ urine protein dipstick (or urinalysis) reading	
	Patients may receive their scheduled dose of bevacizumab and, if they continue to have 2+ urine dipstick (or urinalysis) on repeat analysis, should have a 24-hour urine protein measured prior to the next scheduled dose of bevacizumab.
3+ or greater urine protein dipstick (or urinalysis) reading	
	Patients may have their protein dipstick (or urinalysis) repeated and if still 3+ or greater should not receive their scheduled dose of bevacizumab. The patient should not be dosed until the results of a 24-hour urine protein analysis are available.
Suspend bevacizumab administration for ≥ 2 grams of protein/24 hours and resume when proteinuria is < 2 grams/24 hours (if urine protein decreases to ≤ 1 gm/24 hours, may resume monitoring with dipstick).	
Permanently discontinue bevacizumab if patient develops nephrotic syndrome (Grade 3 proteinuria).	

5.4 Study Drug Inventory and Accountability

In accordance with current Good Clinical Practice (GCP), each study site will keep an accounting of all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the study site. Copies of the study drug accountability record will be provided to the Sponsor.

Study drug must only be dispensed to patients enrolled in the study and only as directed by this protocol. Administration of study drugs will be accurately recorded in each patient's source documents and Case Report Form (CRF).

5.5 Treatment Compliance

Compliance will be ascertained by Investigational Site staff by individual patient assessment and monitoring according to the site standard operating procedures.

5.6 Concomitant Medications and Treatments

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the patient at any time during the study starting at the time that the first dose of study drug was administered through the final study visit assessment. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the CRF.

All inter-current medical conditions will be treated at the discretion of the Investigator according to acceptable community and/or institutional standards of medical care.

The following medications are prohibited during the study:

- Investigational agents
- Other antineoplastic agents, including radiotherapy, chemotherapy, and immunotherapy
- Strong inducers or inhibitors of CYP3A4 or strong UGT1A1 inhibitors, as identified per institutional guidelines. Comprehensive lists can be found at: https://drug-interactions.medicine.iu.edu/
- Drugs known to prolong the QT interval and with a known or potential risk of Torsades de Pointes, as identified per institutional guidelines. Comprehensive lists can be found at: https://www.crediblemeds.org/

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Assessments

The Schedule of Assessments is provided in Table 6-1 and a Schedule of Assessments for PK Sampling is provided in Table 6-2.

Every attempt should be made to have each patient attend each visit as scheduled. Blood collection time points should be adhered to as closely as possible.

Table 6-1 Schedule of Assessments

Assessment/ Procedure	Screening (≤ 28 days prior to enrollment)	Cycle 1 (28-day cycles)		Cycles 2 and Beyond (28-day cycles)		End of Treatment[j] (EOT)
		Day 1	Day 15 ± 3 days	Day 1 ± 3 days	Day 15 ± 3 days	
Informed consent	X					
Confirmation of all eligibility criteria[a]	X					
Tumor tissue sample submission[b]	X					
Medical history[c]	X					X
Prior therapy[d]	X					
Physical examination[e]	X	X	X	X	X	X
ECOG performance status (Appendix 16.2)	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Adverse Event review	X	X	X	X	X	X

Assessment/ Procedure	Screening (≤ 28 days prior to enrollment)	Cycle 1 (28-day cycles)		Cycles 2 and Beyond (28-day cycles)		End of Treatment[j] (EOT)
		Day 1	Day 15 ± 3 days	Day 1 ± 3 days	Day 15 ± 3 days	
Triplicate 12-lead ECG	X	See Table 6-2 for triplicate 12-lead ECG schedule during treatment.				
Clinical chemistry and CEA[f]	X	X		X		
CBC with differential[f]	X	X (Days 1 and 8)	X	X	X	
Blood samples for ctDNA[g]		X		X (Cycles 2 and 3 and every other Cycle after Cycle 3)		X
Disease assessment (radiographic imaging) and re-staging[h]	X			X (prior to start of Cycle 3, and all subsequent odd numbered cycles)		X
Onvansertib[i]		X	X	X	X	
FOLFIRI and bevacizumab		X	X	X	X	

Abbreviations for Table 6-1 and footnotes: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group (performance score); ECG=electrocardiograms; EOS=End of Study; EOT=End of treatment; FFPE=formalin-fixed, paraffin-embedded; MRI=magnetic resonance imaging; PD=progressive disease; TNM=tumor, lymph nodes, metastasis.

[a] Eligibility will be confirmed by submission of an eligibility checklist including de-identified supporting source documents to the CRO Medical Monitor for review and approval. Documentation of a KRAS mutation in exon 2, 3, or 4 as determined by an assay performed in a CLIA-certified laboratory must be provided for inclusion in the study.

[b] Tumor tissue (FFPE) will be collected at study entry for central confirmation of KRAS mutation status and future correlated biomarker studies. If archival FFPE tissue is not available, the patient must undergo a biopsy at screening to obtain tissue for eligibility. Confirmation of KRAS mutation in tumor samples is not required for study eligibility.

[c] Medical history, including recording of relevant medical history, and TNM stage at diagnosis.

[d] Prior treatment start and end dates should be recorded. If intolerance, the reason should be recorded.

[e] Physical examination should include height (at Screening only), weight, vital signs, and general physical examination.

[f] Blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. CBC and clinical chemistry testing (including CEA) may occur up to 48 hours prior to Day 1 and Day 15 (CBC) and Day 1 (clinical chemistry). The Day 8 sample will be collected in Cycle 1 only and may occur up to 24 hours before or after Day 8.

[g] Blood for ctDNA assessment should be collected predose on Day 1 of Cycles 1, 2, 3, and every other Cycle after Cycle 3 (Cycle 5, Cycle 7, Cycle 9, etc), and at EOT. Blood will be collected in three 10-mL Streck tubes (for overnight delivery to Cardiff Oncology).

[h] Radiographic imaging will be obtained during screening, prior to the start of Cycle 3 and at 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. 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. Radiographic imaging should include CT of the chest/abdomen/pelvis with contrast (or MRI if contraindication to intravenous contrast). Radiographic imaging may occur up to 28 days prior to the first dose of onvansertib (study drug).

[i] Patients will take onvansertib on Days 1 to 5 and Days 15 to 19 of each 28-day treatment course. Onvansertib will be dosed in the clinic on Day 1 of each cycle, and Day 5 of Cycles 1, 3, and 5 but otherwise may be taken at home for patient convenience.

[j] EOT assessments should be conducted within 28 days (± 5 days) after the last dose of onvansertib is administered. Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival for 1 year after EOT, at which point they will be considered to have completed the study (EOS).

Table 6-2 Schedule of Assessments for Pharmacokinetic Sampling

Assessment/Procedure	Cycle 1 (28-day cycles)		Cycle 3 (28-day cycles)		Cycle 5 (28-day cycles)	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
PK assessment						
Blood samples for PK assessment[a]	X	X	X	X	X	X
PK assessment blood sampling timepoints[a]	predose	2 to 4 hours postdose	predose	2 to 4 hours postdose	predose	2 to 4 hours postdose
Triplicate 12-lead ECG[b]	X	X	X	X	X	X
Food effect substudy						
Blood samples for food effect substudy[c]				X		X
Food effect substudy blood sampling timepoints[c]				predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 24 hours postdose		predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 24 hours postdose

Abbreviations for Table 6-2 and footnotes: ECG=electrocardiogram; PK=pharmacokinetic.

[a] Blood samples for PK analysis will be obtained during C1D1, C1D5, C3D1, C3D5, C5D1 and C5D5. Samples on C1D1, C3D1, and C5D1 should be collected pre-dose, and samples collected on C1D5, C3D5, and C5D5 should be collected 2 to 4 hrs after the patient has taken the dose.

[b] 12-lead ECGs will be obtained to coincide with PK sampling times. All ECGs should be performed in triplicate. ECG will also be performed at Screening (see Table 6-1).

[c] See Section 6.2.11.4 for details. Note that the PK samples collected for the food effect study on C3D5 and C5D5 may overlap with those collected for general PK analysis (from 2 to 4 hours postdose). One blood sample can be used to satisfy both blood draw requirements.

6.2 Study Procedures

Descriptions of assessments are provided in Sections 6.2.1 through 6.2.13, below. Specific timing requirements for study assessments and procedures are provided in Table 6-1.

6.2.1 Informed Consent and Confirmation of Eligibility Criteria

Patients must be able to provide written informed consent and meet all eligibility criteria (refer to Section 4.1 and Section 4.2) prior to enrollment.

6.2.2 Screening

The Investigator is responsible for keeping a record of all patients screened for entry into the study and those that are subsequently excluded. The reason(s) for patient exclusion from the study must also be recorded.

Each patient (or patient's legal representative if applicable) must provide written informed consent before any study specific assessments may be performed.

Screening assessments should be performed in accordance with the Schedule of Assessments (Table 6-1).

6.2.3 Confirmation of KRAS Mutation Status

Documentation of a KRAS mutation in exon 2, 3, or 4 as determined by an assay performed in a CLIA-certified laboratory must be provided for inclusion in the study.

6.2.4 Tumor Sample Submission

For all patients enrolled under version 2.0 of the protocol, tumor tissue (FFPE) will be collected at study entry. If archival FFPE tissue is not available, the patient must undergo a biopsy to obtain tissue for eligibility. Note that confirmation of KRAS mutation status in the submitted tumor samples is not required for study eligibility.

FFPE tumor tissue requirements:

- Tumor sample requirements:
  - Specimens from the most recent biopsy procedure should be submitted, and must be less than six years old
  - Optimal tumor cross sectional size = 25 mm^2, minimum = 5 mm^2
  - Tumor is required to be at least 20% of the sample by ratio of tumor nuclei to benign nuclei
- FFPE Fixation requirements
  - 10% formalin fixation (neutral buffered) for 6 to 72 hrs, paraffin embedded.
  - No decalcification of the samples (EDTA decalcification is accepted)
- Submit either an FFPE block or unstained slides:
  - If submitting slides: provide a minimum of 10 unstained slides cut at 5 microns on positively charged, unbaked slides and 1 stained hematoxylin and eosin (H&E)

slide. If an H&E slide is not available, provide 11 unstained slides. Submit 10 additional slides if tissue size is < 25mm^2.
- If submitting an FFPE block: choose the block with greatest tumor content. At least one stained H&E slide is required, or an extra unstained slide cut from the block will be generated if H&E slide is not available.

6.2.5 Medical History and Prior Therapy

Medical history includes a thorough review and recording of significant past medical and surgical history, current conditions, concomitant therapies, and TNM stage at diagnosis.

Demographics including age, gender, race, and ethnicity will be recorded.

Prior treatment start and end dates should be recorded. If there was intolerance, the reason should be recorded.

6.2.6 Physical Examinations, Height and Weight, and Vital Signs

A complete physical examination should be conducted including height (at Screening only), weight, vital signs, and general physical examination. A limited physical examination (e.g., symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening in accordance with the Schedule of Assessments (Table 6-1).

6.2.7 Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be assessed in all patients in accordance with the Schedule of Assessments (Table 6-1). The ECOG Performance Status scale and definitions are provided in Appendix 16.2. The ECOG Performance Status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

6.2.8 Concomitant Medication Review

Concomitant medications should be recorded in accordance with the Schedule of Assessments (Table 6-1).

All medications that were used from 28 days prior to enrollment through the end of study participation will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.1.2). Additional guidance regarding concomitant medication is provided in Section 5.6.

6.2.9 Adverse Events

Adverse events should be collected/recorded in accordance with the Schedule of Assessments (Table 6-1).

Detailed guidance for AE reporting is provided in Section 7.

6.2.10 Electrocardiograms

Twelve-lead ECGs will be performed in triplicate at Screening (Table 6-1) and in accordance with the Schedule of Assessments for Pharmacokinetic Sampling (Table 6-2). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF.

6.2.11 Laboratory Assessments

6.2.11.1 Chemistry

Blood samples should be collected for clinical chemistry laboratory testing in accordance with the Schedule of Assessments (Table 6-1). The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT). CEA will also be assessed. Clinical chemistry testing (including CEA) may occur up to 48 hours prior to Day 1. All visits have a ± 3-day window.

6.2.11.2 Hematology

Blood samples for hematology laboratory testing, including complete blood count (CBC) panel, with differential and platelet count should be collected in accordance with the Schedule of Assessments (Table 6-1). CBC may occur up to 48 hours prior to Days 1 and 15 and 24 hours prior to or after Day 8. All visits have a ± 3-day window.

6.2.11.3 Samples for Pharmacokinetic Analysis

Pharmacokinetic samples were obtained from patients in the Phase 1b portion of the study to better characterize PK and allow for population PK and exposure-related analyses to facilitate onvansertib dose selection for the Phase 2 portion of the trial. PK samples will also be collected from all patients enrolled on the Phase 2 portion of the study under version 2.0 of the protocol for further exposure-related analyses of the 15 mg/m^2 dose according to the Schedule of Assessments for PK sampling (Table 6-2). Triplicate ECGs should be obtained as close as possible to the PK blood sampling.

6.2.11.4 Food Effect Substudy

A subgroup of patients (at least 12 patients) enrolled on the Phase 2 portion of the study will participate in a preliminary food effect study. The food effect study will be conducted during Cycles 3 and 5 for the participating patients. All patients should come to the clinic after an overnight fast, and be provided with either water or a fat-containing meal. This substudy will follow a cross-over design, with half of the participating patients (at least 6) taking their onvansertib dose on C3D5 in clinic in a fasted state, with water only. On C5D5, these patients will take their dose 30 minutes after the consumption of a fat-containing meal. PK samples will be drawn immediately before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 24 hours post-dose following both the fasted dose on C3D5 and the fed dose on C5D5 (also see Table 6-2).

The second half of the food effect study participants (at least 6 patients) will undergo the same testing on Cycles 3 and 5, but the order of the fasted and fed states will be reversed; i.e., the second group will take their onvansertib dose in a fed state on C3D5 and will take their dose in a fasted state on C5D5.

6.2.11.5 Samples for Circulating Tumor DNA

Blood samples for ctDNA assessment should be collected prior to study treatment administration and at the time points outlined in the Schedule of Assessments (Table 6-1). Blood will be collected in three 10-mL Streck tubes (for overnight delivery to Cardiff Oncology).

6.2.12 Disease Assessment: Radiographic Imaging

Baseline radiographic imaging may occur up to 28 days prior to administration of the first dose of onvansertib (study drug). CT is the preferred modality, but MRI is acceptable. The same imaging modality should be used throughout the trial.

Radiographic imaging for disease restaging during the treatment period will be obtained at screening, prior to the start of Cycle 3 and at 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 (Table 6-1). Patients who are taken off onvansertib, but remain on FOLFIRI + bevacizumab or any component(s) of the FOLFIRI + bevacizumab regimen are not considered to have started a new anti-cancer therapy and should continue to undergo scans every 8 weeks. Radiographic imaging should include CT of the chest/abdomen/pelvis with contrast (or MRI if the patient has contraindication to intravenous contrast).

6.2.13 End of Treatment/Follow-Up/End of Study

The EOT visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1).

Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival for 1 year after EOT. Follow-up information regarding post-study treatment, including duration of treatment, will be collected approximately every 8 weeks during this 1-year period. Once 1 year of follow-up after EOT has been completed, the patient will be considered to have completed the study (EOS).

Any patient with a suspected study drug-related toxicity at the last follow-up visit must be followed until resolution or until the event is considered irreversible. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the CRF, and in the patient's source documentation.

7 ADVERSE EVENT REPORTING

7.1 Definitions

7.1.1 Adverse Event

An AE is defined in Title 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.2 Unexpected Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

- An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in patient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or patient at immediate risk of death. It

does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.1.4 Definition of Dose-limiting Toxicities

Dose-limiting toxicities are defined as a 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.

7.2 Severity of Adverse Events

Each AE will be graded according to the NCI-CTCAE version 5.0 (Appendix 16.1). In most cases AE terms will be listed in the CTCAE, with grading criteria specific to that term. If the AE is not specifically defined in the CTCAE, it is to be reported using the "Other, specify" term under the appropriate system organ class and graded according to the general CTCAE severity guidelines.

7.3 Relationship of Adverse Events to the Study Drug

The Investigator must attempt to determine if an AE is in some way related to the use of the onvansertib. This causal relationship should be described as follows:

- **Unrelated:** The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease or circumstance.
- **Unlikely:** The event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
- **Possibly:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug, BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication.
- **Probably:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.
- **Definitely:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

7.4 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the first dose of study drug is administered. Patients will be instructed to report all AEs experienced during the study, and patients will be assessed for the occurrence of AEs throughout the study.

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

7.5 Reporting Procedures

7.5.1 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded on the AE form of the CRF and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE. In most cases, date of onset will be adequate; however, for days when the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of onset should also be recorded
2. Specific type of reaction in standard medical terminology
3. Time of resolution of the event (or confirmation ongoing). In most cases, date of resolution will be adequate; however, for events that initiate and resolve on days where the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of resolution should also be recorded
4. Severity/grade of AE. The severity should be rated according to NCI-CTCAE version 5.0 (Appendix 16.1)
5. An assessment should be made of the relationship of the AE to the study drug according to the definitions outlined in Section 7.3.
6. Description of action taken in treating the AE and/or change in study drug administration or dose

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

7.5.2 Reporting of Serious Adverse Events, Including Death

Serious adverse events, including death due to any cause, that occur during this study or within 30 days following the last dose of the study drug, whether or not related to the administration of study drug, must be reported to the Medical Monitor by telephone or email **within 24 hours of learning of the event**.

Serious adverse event forms will be provided by the Sponsor or Sponsor Designated Contract Research Organization. The study site should send the SAE Form to the Medical Monitor as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Medical Monitor is informed of an SAE with preliminary information

obtained, the study site will be instructed to update the SAE Form with additional information, according to the following guidelines:

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available.

During the initial communication, the Medical Monitor will require the following information about the patient and the reported SAE:

1. Patient identification including patient number, initials, and date of birth
2. Date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose
3. Date of last dose of study drugs (i.e., prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose)
4. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event)
5. Date of onset of the AE
6. Date of resolution of the AE (or confirmation ongoing)
7. Severity of the AE (refer to Section 7.2)
8. Assessment of the attribution of the AE to the study drug (refer to Section 7.3)
9. Reason AE is considered serious (according to definition in Section 7.1.3)
10. Whether the AE is expected (refer to Section 7.1)
11. Action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the patient was discontinued from the study)
12. All concomitant medications (including doses, routes, regimens, and indications)
13. Pertinent clinical laboratory testing data
14. Medical history

The Investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drugs and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol

2. Discontinuation or suspension of the study
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study drug-related.

Any SAE that is determined by the Sponsor to be reportable to Food and Drug Administration (FDA) as an Investigational New Drug (IND) Safety Report [as defined in 21 CFR 312.32] will be reported to FDA by the Sponsor within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor within the specified time frames, and will be provided to the Investigator for submission to his or her IRB/IEC.

7.5.3 Other Events Requiring Immediate Reporting

7.5.3.1 Overdose

An overdose is defined as a patient receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol. Any overdose of a study patient with the investigational product, with or without associated AEs/SAEs, is required to be reported to the Medical Monitor within 24 hours of knowledge of the event. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

7.5.3.2 Pregnancy

Should the Investigator become aware of a pregnancy of a female partner of a male participant, the pregnancy should be reported within 24 hours of knowledge of the event. After obtaining the patient's consent (or patient and pregnant partner's consent in the case of a male participant), monitoring of the pregnancy and infant should comply the following procedures:

- If the outcome is an abnormal neonate (infant), as much follow up information as possible to permit evaluation of the case will be collected, including where possible, medical confirmation, medical investigations, and medical record summary details. Follow up should continue for at least 1 year post birth.
- If the outcome is a normal neonate, follow up data should continue for 1 month

8 PATIENT TREATMENT AND STUDY DISCONTINUATION AND SPONSOR TRIAL DISCONTINUATION

8.1 Patient Discontinuation

A patient may choose to stop treatment and/or withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled.

Patients will be discontinued from study drug (onvansertib) treatment if one or more of the following events occur:

1. Clinically significant disease progression
2. Patient refusal to remain on study
3. Non-compliance or inability to comply with protocol requirements by patient
4. Development of unacceptable toxicity (regardless of study drug relationship)
5. Determination by the Investigator that it is no longer safe for the patient to continue therapy.

Patients who have an ongoing AE at the time of treatment discontinuation will continue to be followed until resolution of the event to Grade ≤1 or baseline, or until the event is considered irreversible.

Patients enrolled in the completed Phase 1b portion of the study who discontinued from treatment prior to completing the first treatment cycle (28 days) for any reason other than toxicity, or who did not receive at least 80% of the intended doses, may have been replaced.

8.2 Study Discontinuation

In the completed Phase 1b portion of the study, if 2 or more DLTs were observed in a 3-patient or 6-patient cohort at a given dose level and no lower dose for de-escalation existed, the study would have been stopped and patients and the Investigators would have been notified of termination of the study.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator must notify the IRB/IEC in writing of a premature termination of a study or closure of Investigational Site, and must send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the study from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

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 PK, PD, 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).

9.1.1 Phase 1b

A standard 3 + 3 dose-escalation design was used (Le Tourneau 2012) as described in Section 3.1.2. The dose escalation scheme and DLT evaluation plan used is outlined in Section 3.1.2.1.

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 (up to 6 patients per cohort).

9.1.2 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) of onvansertib on Days 1 to 5 and 15 to 19 of a 28 day cycle concurrently with FOLFIRI + bevacizumab. The definition of the RP2D is provided in Section 3.1.3.1. 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. Selection of 15 mg/m^2 as 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 the study, 15 mg/m^2 was chosen as the RP2D. 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%.

9.2 Statistical Considerations

Enrollment to Phase 1b was in cohorts of 3 patients. The dose escalation rules and DLT criteria are outlined in Section 3.1.2.1.

The definition of the RP2D is provided in Section 3.1.3.1.

9.3 Statistical Analysis

9.3.1 Statistical Analysis of Safety Data

Data from all patients who receive at least 1 dose of any study drug will be included in the safety analysis.

Safety will be assessed primarily based on AEs. The severity of AEs will be graded as mild, moderate, severe, or life-threatening according to NCI-CTCAE version 5.0 (Appendix 16.1). All reported toxicities, regardless of attribution, by toxicity type and maximum grade will be summarized, and sorted by number of patients experiencing the toxicity. The maximum grade consolidates the reports of a given toxicity for a patient over time by taking the maximum across time.

Other safety assessments will include data from concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, ECG measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (e.g., mean, median, range, and standard deviation for continuous data; and frequency for categorical data).

9.3.2 Statistical Analysis for Phase 2

9.3.2.1 Primary Analysis

The primary endpoint for Phase 2 will be objective response rate (ORR). Response rate will be compared with a historical baseline of 15% based on the reported results of FOLFIRI-bevacizumab treatment in second-line setting (Antoniotti 2020; Cremolini 2020). The expected response rate is 30% to reflect a clinically meaningful endpoint for this population with limited treatment options and with presumed limited activity of currently available regimens.

Response rate is defined as a CR or PR according to Investigator's assessment of radiographic imaging results using RECIST v1.1. Patients with missing or unknown response information will be classified as non-responders.

Patients from Phase 2 who receive at least 1 cycle (28 days/4 weeks of treatment) of onvansertib (treated-patient population) will be included in the treated-patient population for efficacy analysis. Patients who have radiographically-confirmed PD prior to the completion of the first cycle will be excluded from this analysis.

The percentage of patients who experience a CR or PR based on RECIST v1.1 will be presented, along with the associated 95% confidence interval.

9.3.2.2 Analysis of Secondary Endpoints

All secondary efficacy endpoint analysis will be carried out in the treated-patient population (i.e., all patients receiving at least 1 cycle of onvansertib). Patients who have radiographically-confirmed PD prior to the completion of the first cycle will be excluded from these analyses.

PFS is defined from the start of treatment to the first observation of PD or death, whichever comes first. The patients who are alive and PD is not observed, PFS will be censored at the date of the latest disease assessment.

DOR is defined from the date of first response (CR or PR) to PD or death, whichever occurs first. This endpoint will be evaluated only in patients who have objective response of CR or PR.

DCR is defined as the number of patients achieving SD, PR, or CR.

Overall survival will be calculated for 1 year following EOT, at which point the patients will be considered to have completed the study (EOS).

Blood samples obtained at baseline and subsequent time points as indicated in the Schedule of Assessments (Table 6-1) will be analyzed for the presence of ctDNA (including KRAS mutations) to assess changes in KRAS allelic burden.

Summary statistics of PK parameters will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided. Log-transformation of exposure measurements may be conducted as needed.

9.3.3 Analysis of Pharmacodynamic and Pharmacokinetic Data (Exploratory Endpoints)

ctDNA isolated from blood samples will be used to monitor changes in KRAS MAF and to evaluate relevant biomarkers correlated with patient response in the treated-patient population. 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 pharmacodynamic analysis will include assessments of pharmacodynamic 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 pharmacodynamic analyses may be conducted as appropriate.

To evaluate the impact of concomitant food intake, descriptive statistics of PK parameters, by fed and fasted state, along with the ratio of geometric means between fed and fasted states will be provided. Summary statistics related to this examination will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided.

Log-transformation of exposure measurements may be conducted as needed for PK and pharmacodynamic associated analyses.

10 ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this study available for monitoring by the Sponsor or its representatives, or by regulatory authorities or health authority inspectors.

Patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study drug and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical Investigators, to other pharmaceutical companies, to the FDA and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region (i.e., US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the patient, appropriate copies for storage off-site will be made.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Collection

All data required by the study protocol will be entered onto CRFs and must be verifiable against source documents. CRFs will be completed for every patient who is enrolled in this study.

Only authorized Investigational Site personnel will enter data on the CRFs. Any corrections to data entered into the CRF will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The CRFs will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date each patient's CRF, verifying that the information is true and correct.

11.2 Study Monitoring

The study will be monitored to evaluate the progress of the study, to verify the accuracy and completeness of the CRFs, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the study monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each patient in the study.

The study monitor will compare the CRF data against source documentation in order to verify its accuracy and completeness. The Investigator and research staff will collaborate with the study monitor to resolve any identified data discrepancies in a timely manner.

The study monitor will record any protocol deviations identified, including, but not limited to, patients that were enrolled even though they did not meet all eligibility criteria, patients who took concomitant medications specifically prohibited by the protocol (refer to Section 5.6), and patients who received the wrong study drug or incorrect dose. The Investigator and research staff will collaborate with the study monitor to identify the reason for each protocol deviation.

The study monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and research staff will collaborate with the study monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

11.3 Data Management

After the CRFs have been reviewed by the study monitor and all identified discrepancies have been identified, the Investigator signed copy of the CRFs will be forwarded to the Clinical Research Organization (CRO) for the study, Data Management. The CRO is responsible for data and safety monitoring. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

All CRF data will be entered into a validated database and an electronic audit study of edits maintained. Laboratory data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

11.4 Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff will cooperate with the auditors and allow access to all patient records supporting the CRFs and other study-related documents.

11.5 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

12 ETHICS

12.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki.

12.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical studies and the protection of human patients.

12.3 Institutional Review Board/Independent Ethics Committee

The protocol, informed consent form (ICF), IB, and any materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to initiation of the study.

Amendments to the protocol will be patient to the same requirements as the original protocol. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

12.4 Informed Consent

No study related procedures, including Screening evaluations, will be performed until the patient has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the patient understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC-approved ICF will be given to each prospective participant. The patients will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the study and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the patient to use and/or disclose Protected Health Information in compliance with Health Insurance Portability and Accountability Act (HIPAA) or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the patient, or the known risks of the study drug change during the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment and to obtain consent from new patients prior to enrollment.

12.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that patient. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor's Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the patient (for whom the departure from protocol was affected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

13 PUBLICATION POLICY

All information and data obtained during the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical study agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

14 PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the patients. The Sponsor is responsible for submitting protocol amendments to the appropriate governing regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to patients.

15 REFERENCES

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https://www.iodine.com/drug/avastin/fda-package-insert

Leucovorin Prescribing Information:
https://www.iodine.com/drug/leucovorin/fda-package-insert

Flourouracil Prescribing Information:
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16 APPENDICES

16.1 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

NCI-CTCAE version 5.0 will be used in this study for AE reporting.

A copy of CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP).

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

16.2 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Note: As previously published.

SUMMARY OF CHANGES: PROTOCOL AMENDMENT v2.0

Version 2.0 Date: 26 Oct 2021

SUMMARY AND RATIONALE

Key reasons for the protocol amendment included:

- The completion of Phase 1b, with the determination of the RP2D and 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 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 CLIA-certified laboratory, is still required.
- Patients must have 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 end of study (EOS) visit, now renamed end of treatment (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.

A detailed table summarizing each revision (previous wording and changes to wording) incorporated into Protocol TROV-054, Version 2.0, dated 11 Oct 2021, and the rationale for each change follows. Corresponding changes have been made to the Protocol Synopsis and List of Abbreviations

and are not listed separately. This table does not contain minor administrative adjustments or corrections that do not have an impact on study conduct or subject safety (e.g., corrections of grammar or spelling).

#	Section(s) V2.0	Previous version	Change	Rationale
1.	Title Page	--Trovagene, Inc. --[redacted] [redacted] --Version number 1.4	--Cardiff Oncology, Inc. --[redacted] [redacted] --Version number 2.0	Change in Sponsor name and contact information, version number
2.	Protocol Approvals	--[redacted] [redacted] --[redacted] [redacted]	--[redacted] [redacted] --[redacted] [redacted]	Change to signatories/titles
3.	Synopsis	--Number of study sites approximately 3 --Principal Investigator: [redacted] [redacted]	--Number of study sites approximately 7 --Principal Investigator: [redacted] [redacted]	Increased number of sites and changed Principal Investigator
4.	Study Administrative Structure	--Investigator: [redacted] --Contract Research Organization: [redacted] --Medical Monitor: [redacted] [redacted]	--Principal Investigator: [redacted] [redacted] --Contract Research Organization: [redacted] --Medical Monitor: [redacted] [redacted]	Edited to reflect administrative updates.
5.	Section 1.1	N/A	**Section 1.1 (Background) Colorectal Cancer** Although an agent specifically targeting mutated KRAS has been approved for the treatment of cancer, this agent (sotorasib, Lumakras) is approved only for the treatment of non-small cell lung cancer (NSCLC) harboring a single specific KRAS mutation (G12C). In clinical trials, the activity of sotorasib in G12C-mutated CRC was substantially lower than that of G12C-mutated NSCLC: ORR of 7.1% and 32.2%, respectively, in a Phase 1 study of sotorasib in patients with solid tumors with the KRAS G12C mutation (Hong 2020). Thus, additional treatments are needed for patients	Background information updated about treatments for cancers with KRAS mutation.

#	Section(s) V2.0	Previous version	Change	Rationale
			with KRAS-mutated CRC.	
6.	Section 1.2	**Section 1.2 (Background) Onvansertib** --Two additional clinical studies…	**Section 1.2 (Background) Onvansertib** --Three additional clinical studies…and Study CRDF-001 (A Phase 2 clinical study of onvansertib in combination with nanoliposomal irinotecan, leucovorin, and 5-FU for the second-line treatment of patients with metastatic pancreatic ductal adenocarcinoma).	Background information updated for onvansertib from two to three studies.
7.	Section 2.1	**Section 2.1 Objectives** **Section 2.1.1 Phase1b** --To evaluate the DLTs and MTD or RP2D of onvansertib… **Section 2.1.2 Phase 2** --To assess the preliminary efficacy of onvansertib… In the Phase 2 segment of the trial, confirmation of a KRAS mutation will be obtained by liquid biopsy during screening to confirm eligibility.	**Section 2.1 Objectives** **Section 2.1.1 Phase1b** --To evaluate the DLTs and MTD of the recommended Phase 2 dose (RP2D) of onvansertib… **Section 2.1.2 Phase 2** --To assess the efficacy and safety of onvansertib …	--Revisions to objectives reflect completion of Phase 1b and need to select RP2D and to fully evaluate both efficacy and safety. --Deleted Phase 2 objective for confirmation of a KRAS mutation by liquid biopsy during screening to confirm eligibility.
8.	Section 2.2.1	**Section 2.2 Endpoints** **Section 2.2.1 Primary** The primary endpoint of Phase 2 is the objective response rate (ORR) by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1) criteria in patients who receive at least 1 cycle (2 courses) of onvansertib…	**Section 2.2 Endpoints** **Section 2.2.1 Endpoints for the Completed Phase 1b Portion of the Study** <u>Primary</u> The primary endpoint of Phase 2 is the objective response rate (ORR) by 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…	--Primary endpoint of Phase 2 clarified from 1 cycle (2 courses) to 1 cycle (28 days/4 weeks of treatment) of onvansertib. --Added population for analysis (treated-patient)..

#	Section(s) V2.0	Previous version	Change	Rationale
9.	Section 2.2.2	**Section 2.2 Endpoints** **Section 2.2.2 Secondary** The following secondary endpoints will be explored in the study population: • Preliminary efficacy defined as complete response (CR) plus partial response (PR) plus SD • AEs, according to the NCI-CTCAE version 5.0 • Progression-free survival (PFS) defined from the date of first drug administration to progression or death, whichever occurs first • Reduction in KRAS allelic burden on liquid biopsies	**Section 2.2 Endpoints** **Section 2.2.2 Endpoints for the Phase 2 Portion of the Study** <u>Secondary</u> The following secondary endpoints will be explored. All efficacy evaluations will be conducted in the treated-patient population: • 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 the 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	--Secondary endpoints of Phase 2 revised to clarify population for efficacy analyses (treated-patient). --Clarified preliminary efficacy endpoint to be a DCR endpoint. --Added endpoints of DOR, OS, and PK of onvansertib in combination with FOLFIRI and bevacizumab

#	Section(s) V2.0	Previous version	Change	Rationale
10.	Section 2.2.2	**Section 2.2 Endpoints** **Section 2.2.3 Exploratory** • Target inhibition of PLK1 based on circulating tumor cells (CTCs) • Use of circulating tumor cells and circulating tumor deoxyribonucleic acid (DNA) to evaluate relevant biomarkers correlated with patient response • Use of archival tumor tissue (if available) to evaluate genomic profiles (DNA/ribonucleic acid [RNA]) associated with patient response	**Section 2.2 Endpoints** **Section 2.2.2 Endpoints for the Phase 2 Portion of the Study** <u>Exploratory</u> • Use of circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA) to evaluate relevant biomarkers correlated with patient response • Use of formalin-fixed, paraffin-embedded (FFPE) tumor tissue to evaluate baseline genomic profiles (DNA/RNA) associated with patient response • Preliminary assessment of food effect	Revised exploratory endpoints, including addition pertaining to food effect
11.	Section 3.1	**3.1 Overall Study Design and Plan** This study will consist of a Screening Period, a Treatment Period conducted in 28-day cycles (there are two 14-day courses of treatment in each 28-day cycle), End-of-Study (EOS) assessments, and a Follow-Up Period. Subjects will continue treatment in the 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.	**3.1 Overall Study Design and Plan** This study will consist of a Screening Period, a Treatment Period conducted in 28-day cycles, End of Treatment (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 study (EOS). Patients will continue treatment in the 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. 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	--Revised two 14-day courses of treatment in each 28-day cycle to 28 day-cycle, added EOT assessments, and defined EOS. --Defined study completion and added criteria for continuing on treatment after radiographic progression --Added a preliminary food effect study in a subgroup of patients.

#	Section(s) V2.0	Previous version	Change	Rationale
			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. A subgroup of patients (at least 12 patients) enrolled in the Phase 2 portion of the study will participate in a preliminary food effect study. See Section 6.2.11.4 for more details.	
12.	Section 3.1.1	**3.1 Overall Study Design and Plan** **Section 3.1.1 Screening Period** In the Phase 2 segment of the trial, confirmation of a KRAS mutation will be obtained by liquid biopsy during screening to confirm eligibility.	**3.1 Overall Study Design and Plan** **Section 3.1.1 Screening Period** In the Phase 2 segment of the study, under protocol version 2.0, FFPE tumor tissue must be available for submission. If archival tissue is not available, patients must undergo a biopsy at screening to obtain tissue for eligibility.	--Deleted requirement for confirmation of a KRAS mutation by liquid biopsy during screening to confirm eligibility. --Added that patient must have FFPE tumor tissue (newly acquired or archival) in order to be enrolled.
13.	Section 3.1.2	**3.1 Overall Study Design and Plan** **Section 3.1.2 Treatment: Phase 1** The starting dose level of onvansertib will be 12 mg/m^2/day for Days 1 to 5 of each 14-day treatment course (there are two 14-day treatment courses in each 28-day cycle).	**3.1 Overall Study Design and Plan** **Section 3.1.2 Treatment Period for the Completed Phase 1b Portion of the Study** The starting dose level of onvansertib was 12 mg/m^2/day for Days 1 to 5 and 15 to 19 of each 28-day treatment cycle.	Dosing and days used were clarified.
14.	Section 3.1.2.1	**3.1 Overall Study Design and Plan** **Section 3.1.2.1 Dose Escalation and Dose-limiting Toxicity** • If 2 or more DLTs are observed in a 3-patient or 6-patient cohort at a given dose level, the MTD has been exceeded, dose escalation will be stopped, and up to 3 additional patients will be enrolled at the next lower dose, if it exists, unless 6 patients have already been treated at that prior dose.	**3.1 Overall Study Design and Plan** **Section 3.1.2.1 Dose Escalation and Dose-limiting Toxicity** • If 2 or more DLTs were observed in a 3-patient or 6-patient cohort at a given dose level, the MTD was deemed to have been exceeded, dose escalation was stopped, and up to 3 additional patients were enrolled at the next lower dose.	Deleted the part about unless 6 patients have already been treated at that prior dose as this did not occur.

#	Section(s) V2.0	Previous version	Change	Rationale
15.	Section 3.1.3	**3.1 Overall Study Design and Plan** **Section 3.1.3 Treatment: Phase 2** Phase 2 will start once the RP2D is identified. Final determination of the RP2D will be based on evaluating all available data from the dose escalation Phase 1b portion of the trial, including low-grade, but chronic toxicities, dose reductions and/or missed doses of onvansertib. In the Phase 2 segment of the trial, confirmation of a KRAS mutation will be obtained by liquid biopsy during screening to confirm eligibility.	**3.1 Overall Study Design and Plan** **Section 3.1.3 Treatment Period for the Phase 2 Portion of the Study** Phase 2 commenced once 15 mg/m^2 was selected as the RP2D (is also the MTD). The sample size of the Phase 2 portion of the study has been increased from 26 patients to approximately 80 patients in order to further evaluate the safety and efficacy of the onvansertib 15 mg/m^2 dose.	--Revised to show that 15 mg/m^2 was selected as the RP2D (is also the MTD). --Sample size for Phase 2 increased from 26 to approximately 80 patients. --Deleted requirement for confirmation of a KRAS mutation by liquid biopsy during screening to confirm eligibility.
16.	Section 3.1.3.1	**3.1 Overall Study Design and Plan** **Section 3.1.3.1 Recommended Phase 2 Dose** The RP2D is the highest dose at which 1 or fewer of 6 patients experience a DLT during Cycle 1 of therapy (the definition of DLT is provided in Section 7.1.4). If 2 or more DLTs are observed at the next highest dose, this dose is also referred to as the MTD. If no higher dose level has been studied, the RP2D is also referred to as the highest treatment dose (HTD).	**3.1 Overall Study Design and Plan** **Section 3.1.3.1 Recommended Phase 2 Dose** The RP2D is 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 7.1.4). 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 selected as the RP2D (and is also the MTD).	Revised to reflect RP2D (15 mg/m^2/day and is also the MTD) with completion of Phase 1b.
17.	3.1.3.2	**3.1 Overall Study Design and Plan** **Section 3.1.3.2 Dose Modifications** In Phase 1b and 2, should a subject experience a Grade ≥2 neutropenia or neutropenic fever during treatment, a dose modification will be allowed for the treatment component(s) deemed probable	**3.1 Overall Study Design and Plan** **Section 3.1.3.2 Dose Modification Guidelines** For those patients enrolled in the Phase 2 portion of the study who receive the optional (at Investigator's discretion) 5-FU bolus and leucovorin, occurrence of a	--Revised so that 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 provided if

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		for the etiology of the toxicity. In the case of the 5-FU component, in subsequent cycles and according to institutional guidelines, dose modification including elimination of the 5-FU bolus infusion will be allowed. Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2 and will be based on dose modification guidelines provided in Table 5-4; additional details are provided in the relevant package insert(s) (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; (Avastin Prescribing Information). Any necessary dose level reductions for onvansertib or for FOLFIRI and bevacizumab should follow the dose levels outlined in Table 5-1 and Table 5-3.	Grade ≥ 2 neutropenia or neutropenic fever that is determined to be caused or exacerbated by the administration of the 5-FU bolus and/or leucovorin may have the 5-FU bolus and/or leucovorin eliminated in subsequent cycles, at the Investigator's discretion. If individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios. Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2; additional details are provided in the relevant package insert(s) (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information).	intolerance of individual drugs from the FOLFIRI + bevacizumab regimen is observed.
18.	Section 3.1.4	**Section 3.1.4 End of Study** The EOS visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6 1). The EOS visit is described further in Section 6.2.12.	**Section 3.1.4 End of Treatment** The EOT visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1). The EOT visit is described further in Section 6.2.13.	Study visit following last dose of onvansertib, previously referred to as the end of study (EOS) visit, now renamed end of treatment (EOT) visit.
19.	Section 3.1.5	**Section 3.1.4 End of Study** The EOS visit should occur within 28 days (± 5 days) after the last dose of onvansertib	**Section 3.1.5 Follow-up and End of Study** Patients (any ongoing from Phase 1b and those from Phase 2) will be followed for	Added additional information regarding follow-up (e.g., who will be followed, radiographic

#	Section(s) V2.0	Previous version	Change	Rationale
		is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1). The EOS visit is described further in Section 6.2.12.	overall survival 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 anti-cancer 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).	scanning, collection of new-anti-cancer treatment, definition of completion of study [EOS] as once patients have been followed for 1 year after EOT).
20.	Section 3.2	**Section 3.2 Study Duration** The Screening Period will be up to 28 days prior to the first dose of onvansertib. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until PD or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion.	**Section 3.2 Study Duration** The Screening Period will be up to 28 days prior to the first dose of onvansertib. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until PD or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival 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 anti-cancer treatment, such as type of treatment and duration of treatment, will be collected approximately every 8 weeks	Added additional information regarding follow-up, radiographic scanning during follow-up, collection of new-anti-cancer treatment, and definition of completion of study (EOS) as being once patients have been followed for 1 year after EOT.

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			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).	
21.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #2: In the Phase 2 segment of the trial, confirmation of a KRAS mutation will be obtained by liquid biopsy during screening to confirm eligibility.	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #2: N/A	Removed part of Criterion #2 during Phase 2 for confirmation of a KRAS mutation by liquid biopsy during screening to confirm eligibility.
22.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criteria #13: If archival tumor tissue is available, the subject must give consent to having it used for future correlative marker assays. Confirmation of the availability and consent for use of archival tumor tissue does not have to occur prior to enrollment. Refer to Section 6.2.10 for guidelines regarding provision of archival tumor tissue samples.	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #3: FFPE tumor tissue must be available for submission to a central laboratory in order for a patient to be eligible. If no archival tissue biopsy is available the patient must have a biopsy obtained at screening. Refer to Section 6.2.4 for guidelines regarding provision of tumor tissue samples.	Deleted Inclusion Criteria #13 and replaced with Inclusion Criteria #3. Patient must have FFPE tumor tissue (newly acquired or archival) in order to be eligible.
23.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #6: Subject is not receiving any other cancer therapy. Patients participating in surveys or observational studies are allowed.	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #7: Subject is not receiving any other standard-of-care or experimental cancer therapy. Patients participating in non-interventional surveys or observational studies are allowed.	Clarification
24.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #7: Has failed treatment or is intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab. a. All patients must have received a minimum of 6 weeks of the first-line regimen that included oxaliplatin and a fluoropyrimidine with or without bevacizumab in the same cycle. Treatment failure is defined as	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #8: Has failed treatment or is intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab. a. Patients must have had systemic therapy within 180 days of the screening visit, but can have no anti-cancer therapy within 28 days of the planned first day of treatment on study.	Inclusion subcriteria were revised and clarified, including new additions.

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		radiologic progression during or < 6 months after the last dose of first-line therapy. b. Patients who show tumor progression while on maintenance therapy with a fluoropyrimidine with or without bevacizumab after prior fluoropyrimidine-oxaliplatin with or without bevacizumab induction therapy are eligible. Rechallenge with oxaliplatin is permitted and will be considered part of the first-line regimen for metastatic disease, with both initial oxaliplatin treatment and subsequent rechallenge being considered as one regimen. c. Patients who received oxaliplatin/fluoropyrimidine-based neoadjuvant or adjuvant therapy and have disease recurrence or progression > 6 months from their last dose of neoadjuvant or adjuvant treatment (or > 6 months from surgery if no adjuvant therapy was administered) will be required to receive fluoropyrimidine/oxaliplatin-based therapy with or without bevacizumab for metastatic disease. d. For patients with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen. e. Patients who discontinued first-line therapy because of toxicity may be enrolled for as long as progression occurred < 6 months after the last dose of first-line therapy.	b. Patients must have received oxaliplatin based chemotherapy with or without bevacizumab (≥ 6 weeks in duration). Patients who received maintenance therapy with fluoropyrimidines are eligible with or without rechallenge with oxaliplatin in combination with fluoropyrimidines. c. Patients who received oxaliplatin/fluoropyrimidine-based neoadjuvant or adjuvant therapy and have disease recurrence or progression > 6 months from their last dose of neoadjuvant or adjuvant treatment (or > 6 months from surgery if no adjuvant therapy was administered) will be required to have received fluoropyrimidine/oxaliplatin-based therapy with or without bevacizumab as first-line treatment for metastatic disease. d. Patients must not have received prior irinotecan. e. For patients with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen for advanced disease. f. Patients who discontinued first-line therapy because of toxicity are eligible as long as progression occurred < 6 months after the last dose of first-line therapy.	

#	Section(s) V2.0	Previous version	Change	Rationale
25.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #9: For a male or a woman of child-bearing potential (WOCBP): Must agree to use contraception…	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #10: For a woman of child-bearing potential (WOCBP) or a male with a female partner who is a WOCBP: Must agree to use contraception…	Revised males to males with a female partner who is a WOCBP.
26.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #11: Imaging computed tomography (CT)/magnetic resonance imaging (MRI) of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 28 days prior to the first dose of onvansertib. Only patients with measurable disease are eligible for enrollment.	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #12: Imaging computed tomography (CT)/magnetic resonance imaging (MRI) of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 28 days prior to the first dose of onvansertib. Only patients with measurable disease as defined per RECIST v1.1 are eligible for enrollment. CT is the preferred imaging modality, but MRI is also accepted.	Revised to specify measurable disease as per RECIST v 1.1 and that CT is the preferred imaging modality, but MRI is accepted.
27.	Section 4.1.1	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #12, Table 4-1 Acceptable Organ Function: --Bilirubin: ≤ 1.5 ULN OR ≤ 2.0 ULN in presence of liver metastases	**Section 4.1.1 Inclusion Criteria** Inclusion Criterion #13, Table 4-1 Acceptable Organ Function: --Bilirubin: ≤ 1.5 ULN OR ≤ 2.0 mg/dL in presence of liver metastases	Revised bilirubin criterion.
28.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #2: Anti-cancer chemotherapy or biologic therapy administered within 4 weeks prior to the first dose of study drug.	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #2: Anti-cancer chemotherapy or biologic therapy administered within 28 days prior to the first dose of study drug.	Revised from 4 weeks to 28 days
29.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #4: Major surgery within 6 weeks prior to randomization.	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #4: Major surgery within 6 weeks prior to enrollment.	Revised from randomization to enrollment.
30.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #5: Untreated brain metastasis.	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #5: Untreated or symptomatic brain metastasis.	Added symptomatic brain metastasis.

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31.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** N/A	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #9b: Known active infection with SARS-CoV-2	Added known active infection with SARS- CoV-2.
32.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #13: Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix,…	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #13: Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix or prostate,…	Added that curatively treated in-situ cancer of the prostate is an exception to exclusion of other malignancies.
33.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #17: In the case of potentially correctible causes of QT prolongation, (e.g., medications, hypokalemia),…	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #17: In the case of potentially correctible causes of QT prolongation that are readily corrected (e.g., medications, hypokalemia),…	Clarification
34.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #18: Planned concomitant use of medications known to prolong the QT/QTc interval.	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #18: Planned concomitant use of medications known to prolong the QT/QTc interval according to institutional guidelines.	Clarification
35.	Section 4.1.2	**Section 4.1.2 Exclusion Criteria** N/A	**Section 4.1.2 Exclusion Criteria** Exclusion Criterion #21: Use of strong CYP3A4 or UGT1A1 inhibitors or strong CYP3A4 inducers. Patients currently receiving these agents who are able to switch to alternate therapy are not excluded. Inhibitors should be stopped at least 1 week prior to the first dose of protocol therapy and inducers should be stopped at least 2 weeks prior to initiation of protocol therapy.	Added exclusion criteria for use of strong CYP3A4 or UGT1A1 inhibitors or strong CYP3A4 inducers.
36.	Section 4.2	**4.2 Removal of Patients From Therapy or Assessment** • Entry into another investigational clinical study or start of additional anticancer therapy	**4.2 Removal of Patients From Therapy or Assessment** • Entry into another investigational clinical study or start of additional anticancer therapy (participation in	--Clarifications --Revised EOS to EOT --Guidance was provided if intolerance of individual drugs from the FOLFIRI + bevacizumab regimen is

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		• In the event that a patient is withdrawn from the study,… • An EOS reason must be recorded If a patient is discontinued from the study for any reason, every effort must be made to perform all EOS assessments (Section 6.1)… N/A	non-interventional surveys or observational studies are allowed) • In the event that a patient is withdrawn from treatment and/or the study,… • An EOT reason must be recorded If a patient is discontinued from treatment or the study for any reason, every effort must be made to perform all EOT assessments (Section 6.1)… If individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios. See also Sections 3.1.3.2 and 5.3.	observed.
37.	Section 5.2.1	**5.2.1 Onvansertib Administration** The starting dose of onvansertib will be 12 mg/m^2 administered PO on Day 1 through Day 5 every 14 days (there are two 14-day courses of treatment in each 28 day cycle). Table 5-1 Dose Levels of Onvansertib, all rows under Frequency said Days 1 to 5 of each 14-day course.	**5.2.1 Onvansertib Administration** <u>Completed Phase 1b Portion of the Study</u> The starting dose of onvansertib was 12 mg/m^2 administered PO on Day 1 through Day 5 and Day 15 through Day 19 of each 28-day treatment cycle. Table 5-1 Dose Levels of Onvansertib in the Completed Phase 1b Portion of the Study, all rows under Frequency say Days 1 to 5 and 15 to 19 of each 28-day cycle.	Clarification
38.	Section 5.2.1	**5.2.1 Onvansertib Administration** N/A	**5.2.1 Onvansertib Administration** <u>Phase 2 Portion of the Study</u>	Subdivided into completed Phase 1b and Phase 2 sections.

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			Based on results of the Phase 1b portion of this study, 15 mg/m^2/day was selected as the RP2D (also the MTD). The RP2D and dose modifications for onvansertib for the Phase 2 portion of the study are shown in Table 5-2. Note: Table 5-2 is not reproduced in this Summary of Changes, but shows RP2D of 15 mg/m^2 with dose reductions to 12 mg/m^2 QD and 6 mg/m^2 QD with all frequency as Days 1 to 5 and 15 to 19 of each 28-day cycle.	New subsection added for Phase 2 dosing, along with corresponding table.
39.	Section 5.2.1.1	**Section 5.2.1.1 Food Restrictions** N/A	**Section 5.2.1.1 Food Restrictions** See Section 6.2.11.4 for information on PK food effect substudy.	Added cross-reference to section on food effect substudy
40.	Section 5.2.1.2	**5.2.1.2 Dose Rounding** Dose rounding is to the nearest 5 mg, rounded up for dose calculations ending in 0.5 to 0.9. (For example, if 18 mg/m^2 dose is calculated at 32.4 mg, the dose would be rounded down to 30 mg, provided as one 20 mg capsule and two 5 mg capsules of onvansertib).	**5.2.1.2 Dose Rounding** Dose rounding is to the nearest 5 mg, rounded up for dose calculations ending in 0.5 to 0.9. For example, at the RP2D of 15 mg/m^2 the daily dose is calculated at 27 mg and would be rounded up to 30 mg, provided as one 20 mg capsule and two 5 mg capsules of onvansertib.	Dose rounding revised to reflect RP2D dose of 15 mg/m^2
41.	Section 5.2.2	**5.2.2 FOLFIRI and Bevacizumab Administration** Note: Table 5-2, Dose Levels of FOLFIRI and Bevacizumab, is not reproduced in this Summary of Changes, but shows frequency of bevacizumab, irinotecan, leucovorin, and 5-FU (bolus) as being given on Day 1 of each 14-day course and 5-FU infusion as beginning on Day 1 of each 14-day course. A Note to table said: One cycle is 28 days. There are two 14-day courses of treatment in each 28 day cycle.	**5.2.2 FOLFIRI and Bevacizumab Administration** <u>Completed Phase 1b Portion of the Study</u> Note: Table 5-3 (revised from Table 5-2), Doses of FOLFIRI and Bevacizumab in the Completed Phase 1b Portion of the Study, is not reproduced in this Summary of Changes, but shows frequency of bevacizumab, irinotecan, leucovorin, and 5-FU (bolus) as being given on Days 1 and 15 of each 28-day cycle and 5-FU infusion	--Clarifications --Subdivided into completed Phase 1b and Phase 2 sections. For Phase 1b, clarified dosing in FOLFIRI and Bevacizumab Administration section for Completed Phase1b Portion of the Study.

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			as beginning on Days 1 and 15 of each 28-day cycle. --Deleted Note: One cycle is 28 days. There are two 14-day courses of treatment in each 28 day cycle. --Footnote "a" was added to 5-FU bolus that dose modifications including elimination of the 5-FU bolus infusion were allowed.	
42.	Section 5.2.2	**5.2.2 FOLFIRI and Bevacizumab Administration** N/A	**5.2.2 FOLFIRI and Bevacizumab Administration** Phase 2 Portion of the Study After evaluation of safety data from the Phase 1b portion of the study, the 5-FU bolus and leucovorin will be optional, at the investigator's discretion, for any patients in the Phase 2 portion of the study enrolled under version 2.0 of the protocol. All patients in the Phase 2 portion will receive the 46-hour 5-FU continuous infusion. Note: Table 5-4, Doses of FOLFIRI and Bevacizumab in the Phase 2 Portion of the Study, is not reproduced in this Summary of Changes, but provides dosing guidelines for drugs in FOLFIRI and bevacizumab	Subdivided into completed Phase 1b and Phase 2 sections. For Phase 2, added new text and dosing table in FOLFIRI and bevacizumab administration section.
43.	Section 5.3	**Section 5.3 Dose Modifications** In Phase 1b and 2, should a subject experience a Grade ≥2 neutropenia or neutropenic fever during treatment, a dose modification will be allowed for the treatment component(s) deemed probable for the etiology of the toxicity. In the case of the 5-FU component, in subsequent cycles and according to institutional guidelines, dose modification including elimination of the 5-FU bolus infusion will be allowed.	**Section 5.3 Dose Modifications** For those patients enrolled in the Phase 2 portion of the study (this was also applied to patients enrolled in the Phase 1b portion of the study) who receive the 5-FU bolus and leucovorin, occurrence of a Grade ≥ 2 neutropenia or neutropenic fever that is determined to be caused or exacerbated by the administration of the 5-FU bolus and/or leucovorin may have the 5-FU bolus and/or leucovorin eliminated in subsequent cycles, at the Investigator's discretion.	--Clarification to dose modifications, including that leucovorin was added to 5-FU bolus, both of which may be eliminated in subsequent cycles. --Info on DLTs was deleted as not applicable to Phase 2.

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		Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2 and will be based on dose modification guidelines provided in Table 5 4; additional details are provided in the relevant package insert (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; (Avastin Prescribing Information). Any necessary dose level reductions for onvansertib or for FOLFIRI and bevacizumab should follow the dose levels outlined in Table 5-1 and Table 5-3. For any Grade 1 and 2 nausea or vomiting, maximize the antiemetic regimen prescribed to the subject. For Grade 3 nausea or vomiting, reduce irinotecan for the next cycle. For each subsequent cycle, the subject may continue irinotecan at the previous dose level, provided nausea has resolved to Grade 2 or 1. For Grade 4 nausea or vomiting, discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level. If one of the drugs (onvansertib or FOLFIRI or bevacizumab) must be discontinued based on Investigator discretion or due to toxicity, patients may continue to receive the other drug(s) alone. If 2 or more DLTs are observed in a 3-patient or 6-patient cohort at a given dose level and no lower dose for de-escalation exists, the study will be stopped and subjects and investigators will be notified of termination of the study.	Dose modifications for onvansertib are allowed in accordance with Section 5.3.1. Dose adjustments for FOLFIRI and bevacizumab are allowed in accordance with Section 5.3.2 and will be based on dose modification guidelines provided in Table 5-6 and Table 5-7; additional details for FOLFIRI and bevacizumab are provided in the relevant package insert (PI). As per Table 5-7, for any Grade 1 and 2 nausea or vomiting, maximize the antiemetic regimen prescribed to the patient. For Grade 3 nausea or vomiting, reduce irinotecan for the next cycle. For each subsequent cycle, the patient may continue irinotecan at the previous dose level, provided nausea has resolved to Grade 2 or 1. For Grade 4 nausea or vomiting, discontinue 5-FU bolus (if using) and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite 2 treatments with adequate (combination) antiemetic therapy. As per Sections 3.1.3.2 and 4.2, if individual drugs from the FOLFIRI + bevacizumab regimen are discontinued because of patient intolerance, patients may remain on onvansertib and the remaining drugs from the FOLFIRI + bevacizumab regimen, provided that either 5-FU or irinotecan (or both) is continued. Onvansertib may not be administered as a single agent or with bevacizumab alone, as there are no data to support either of these treatment scenarios.	

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44.	Section 5.3.1.1	**Section 5.3.1 Onvansertib** **5.3.1.1 Dose Delays** Patients who experience any Grade 2 or higher AE considered related to the study drug (i.e., adverse reaction or suspected adverse reaction according to the criteria in Section 7.1.2) will have their next dose of onvansertib held until all study drug-related toxicities have improved to Grade 1 or to Baseline. If the AE does not resolve to Grade 1 or less or to Baseline within 2 weeks, the patient will be discontinued from study treatment. Dose delays do not alter the Schedule of Assessments. If pharmacokinetic or pharmacodynamic studies are scheduled at the time of a dose delay, these will be delayed, and should be rescheduled by the Investigator and Sponsor. If a patient forgets to take their dose of study drug on any day during Days 1 to 5 of the cycle, they will have the opportunity to take the scheduled dose within 4 to 6 hours of the original scheduled time on that same day. If a patient misses a dose of study drug on any day during Days 1 to 5 of the cycle, they will not be able to make up the missed dose on the next day or move the Day 1 to 5 dosing schedule out to additional consecutive days (e.g., Day 6, etc.). If onvansertib is vomited, participants should not retake drug, but should take it instead at the next scheduled time.	**Section 5.3.1 Onvansertib Dose Modifications** **5.3.1.1 Dose Delays** Patients who experience any Grade 3 or higher AE considered related to onvansertib (i.e., adverse reaction or suspected adverse reaction according to the criteria in Section 7.3) will have their next dose of onvansertib held until all study drug-related toxicities have improved to Grade 1 or to Baseline. If the AE does not resolve to Grade 1 or less or to Baseline within 2 weeks, the patient will be discontinued from treatment, unless the investigator believes it is in the patient's best interest to delay more than 2 weeks and has discussed the case and obtained approval of the Medical Monitor to restart the treatment after a delay longer than 2 weeks. In the Phase 2 portion of the trial, if a patient experiences recurrent Grade 3 or higher toxicity related to onvansertib at the lowest allowed onvansertib dose (6 mg/m^2), treatment with onvansertib must be discontinued as no further dose reductions are allowed. Dose delays do not alter the Schedule of Assessments. If pharmacokinetic or pharmacodynamic studies are scheduled at the time of a dose delay, these will be delayed, and should be rescheduled by the Investigator and Sponsor. If treatment is delayed for 7 days, e.g., Cycle 1 Day 15 must be delayed to Day 22, then the numbering of the subsequent dose will not change, e.g., the treatment given on Day 22 will be considered the Cycle 1 Day 15 dose. However, if treatment is delayed for 14 days or greater, then the next	--Clarifications --Revised 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. --Deleted consideration of restarting onvansertib after AE resolution must be discussed with the Medical Monitor. --Changed cross-reference to relationship of adverse events to the study drug section instead of unexpected adverse events section. --Added allowance for continuing treatment per investigator discretion if AE does not resolve to Grade 1 or less or to Baseline within 2 weeks. --Rules for numbering of dose cycles were clarified.

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			treatment will be considered Day 1 of the subsequent cycle. Examples: if Cycle 1 Day 15 is delayed by 14 days, the next treatment will be considered the Cycle 2 Day 1 treatment. If Cycle 2 Day 1 is delayed by 14 days, the next treatment will still be considered the Cycle 2 Day 1 treatment. If a patient forgets to take their dose of study drug on any day during Days 1 to 5 or 15 to 19 of the cycle, they will have the opportunity to take the scheduled dose within 4 to 6 hours of the original scheduled time on that same day. If a patient misses a dose of study drug on any day during Days 1 to 5 or Days 15 to 19 of the cycle, they will not be able to make up the missed dose on the next day or move the Day 1 to 5 or Day 15 to 19 dosing schedule out to additional consecutive days (e.g., Day 6, Day 20, etc.). If onvansertib is vomited, participants should not retake drug, but should take it instead at the next scheduled time.	
45.	Section 5.3.1.2	**Section 5.3.1 Onvansertib** **5.3.1.2 Dose Reduction** If a DLT resolves to Grade 1 or less, the dose of onvansertib will be reduced to the next lower dose level in subsequent cycles based on Investigator discretion.	**Section 5.3.1 Onvansertib** **5.3.1.2 Dose Reduction** <u>Completed Phase 1b Portion of the Study</u> If a DLT resolved to Grade 1 or less, the dose of onvansertib was reduced to the next lower dose level in subsequent cycles based on Investigator discretion (see Section 5.2.1, Table 5-1). <u>Phase 2 Portion of the Study</u> Dose reduction levels for onvansertib in the Phase 2 portion of the study are outlined in Section 5.2.1, Table 5-2. Onvansertib-related hematologic AEs	--Revised to show separate completed Phase 1b and Phase 2 dose reduction guidance. --Added table for dose reduction for onvansertib-related hematologic adverse events.

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			require modifications to the onvansertib dose per Table 5-5: **HEMATOLOGIC TOXICITIES: Dose modifications recommended for the next treatment cycle based on toxicity experienced during a previous cycle (i.e., after Days 1-5 or 15-19 of any cycle):** **--Grade 3 or 4 neutropenia or thrombocytopenia:** 1st occurrence, Continue onvansertib at current dose level, 2nd occurrence, Continue onvansertib at one lower dose level **Febrile neutropenia (defined as ANC < 1000/µL and T ≥ 38.5°C):** 1st occurrence, Continue onvansertib at current dose level, 2nd occurrence, Continue onvansertib at one lower dose level	
46.	Section 5.3.1.3	**Section 5.3.1 Onvansertib** **5.3.1.3 Dose Escalation** Once a dose level of onvansertib has cleared the DLT safety window, patients continuing on treatment may have their dose increased to that next higher dose level at the discretion of the investigator. For example, if the onvansertib 15 mg/m^2 dose level has been cleared for safety, patients on treatment at onvansertib 12 mg/m^2 may have their dose of onvansertib increased to 15 mg/m^2.	**Section 5.3.1 Onvansertib** **5.3.1.3 Dose Escalation** Completed Phase 1b Portion of the Study In the completed Phase 1b portion of the study, once a dose level of onvansertib had cleared the DLT safety window, patients continuing on treatment were allowed to have their dose increased to that next higher dose level at the discretion of the Investigator. For example, if the onvansertib 15 mg/m^2 dose level had been cleared for safety, patients on treatment at onvansertib 12 mg/m^2 were permitted to have their dose of onvansertib increased to 15 mg/m^2.	Revised to reflect completion of Phase 1b.
47.	Section 5.3.2	**5.3.2 FOLFIRI and Bevacizumab Dose Modifications** Should a subject experience a Grade ≥ 2	**5.3.2 FOLFIRI and Bevacizumab Dose Modifications** Should a patient experience a Grade ≥ 2	--Revised to allow for continuation of all other study drugs if irinotecan is

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		neutropenia or neutropenic fever during treatment, a dose modification will be allowed for the treatment component(s) deemed probable for the etiology of the toxicity. In the case of the 5-FU component, in subsequent cycles and according to institutional guidelines, dose modification including elimination of the 5-FU bolus infusion will be allowed. Dose adjustments for FOLFIRI and bevacizumab are allowed and should be in accordance with the Dose Modification Guidelines (Table 5-4). Any necessary dose reductions for FOLFIRI should follow the dose levels outlined in **Error! Reference source not found.**. Additional details for FOLFIRI and bevacizumab are provided in the relevant package insert (PI) (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information). Note: Table 5-3, Dose Reduction Levels of FOLFIRI, is not reproduced in this Summary of Changes, but had only 2 dose reduction columns and no footnotes.	neutropenia or neutropenic fever during treatment, a dose modification will be allowed for the treatment component(s) deemed probable for the etiology of the toxicity. Any necessary dose reductions for FOLFIRI should follow the dose levels outlined in Table 5-6, and should be in accordance with the dose modification guidelines presented in Table 5-7. Additional details for FOLFIRI and bevacizumab are provided in the relevant package insert (Leucovorin Prescribing Information; Fluorouracil Prescribing Information; Camptosar Prescribing Information; Avastin Prescribing Information). Note: if irinotecan is discontinued due to toxicity, all other study drugs may be continued (5-FU, bevacizumab, and onvansertib). Note: Table 5-6, Dose Reduction Levels of FOLFIRI, is not reproduced in this Summary of Changes, but revisions included adding a third dose reduction as an option for irinotecan and 5-FU infusion. Footnotes were added to this table pertaining to 5-FU and leucovorin.	discontinued. --Dosing table was revised to add a third dose reduction as an option for irinotecan and 5-FU infusion. Footnotes were added to this table pertaining to 5-FU and leucovorin.
48.	Section 5.3.2, Table 5-7	**5.3.2 FOLFIRI and Bevacizumab Dose Modifications** **Table 5-4, Dose Modification Guidelines for FOLFIRI and Bevacizumab:** **--HEMATOLOGIC TOXICITIES: Dose modifications recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 of any cycle):**	**5.3.2 FOLFIRI and Bevacizumab Dose Modifications** **Table 5-7, Dose Modification Guidelines for FOLFIRI and Bevacizumab:** **--HEMATOLOGIC TOXICITIES**: **Dose modifications recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 or 15 of any cycle):**	Clarifications made to dosing modification guidelines for certain toxicities.

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		Grade 3 or 4 neutropenia or thrombocytopenia --Continue onvansertib at one lower dose level **--Febrile neutropenia (defined as ANC < 1000/µL and T ≥ 38.5°C):** **--**If fever resolves, and counts recover to ANC ≥ 1000/µL and platelets ≥ 75,000/mm^3 within (sic, missing parameters) --Continue onvansertib at one lower dose level **--Grade 2 diarrhea:** Discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next cycle. For each subsequent cycle, … **--Grade 2 mucositis**: May discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next cycle…. **--Grade 3 nausea or vomiting:** Reduce irinotecan one dose level for the next cycle…. **--Grade 4 nausea or vomiting:** Discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite two treatments with adequate (combination) antiemetic therapy. The use of aprepitant is prohibited for those patients receiving FOLFIRI.	**Grade 3 or 4 neutropenia or thrombocytopenia** --N/A (deleted) **--Febrile neutropenia (defined as ANC < 1000/µL and T ≥ 38.5°C):** **--**If fever resolves, and counts recover to ANC ≥ 1000/µL and platelets ≥ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows:… -- N/A (deleted) **--Grade 2 diarrhea:** Discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next dose. For each subsequent dose, … **--Grade 2 mucositis**: May discontinue 5-FU bolus (if using). Reduce 5-FU infusion and irinotecan one dose level for the next dose…. **--Grade 3 nausea or vomiting:** Reduce irinotecan one dose level for the next dose…. **--Grade 4 nausea or vomiting:** Discontinue 5-FU bolus (if using) and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite 2 treatments with adequate (combination) antiemetic therapy.	
49.	Section 5.6	**Section 5.6 Concomitant Medications and Treatments**	**Section 5.6 Concomitant Medications and Treatments**	--Clarifications --New prohibited medications

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		The following medications are prohibited during the study: • Investigational agents • Other antineoplastic agents • Radiotherapy • Chemotherapy • Immunotherapy • Digoxin, digitoxin, and other digitalis drugs • Fludrocortisone acetate (Florinef)	The following medications are prohibited during the study: • Investigational agents • Other antineoplastic agents, including radiotherapy, chemotherapy, and immunotherapy • Strong inducers or inhibitors of CYP3A4 or strong UGT1A1 inhibitors, as identified per institutional guidelines. Comprehensive lists can be found at: https://drug-interactions.medicine.iu.edu/ • Drugs known to prolong the QT interval and with a known or potential risk of Torsades de Pointes, as identified per institutional guidelines. Comprehensive lists can be found at: https://www.crediblemeds.org/	added and others deleted.
50.	Table 6-1	**Table 6-1 Schedule of Assessments** --Column headers for both Cycles 1 and 2: Treatment Course (two courses per cycle) --Column headers for Day 1 (first day of first course) and Day 15 ± 3 days (first day of second course) --Column header: End of Study with corresponding footnote "j" about radiographic imaging and footnote "m" that read: EOS assessments should be conducted within 28 days (± 5 days) after the last dose of onvansertib is administered.	**Table 6-1 Schedule of Assessments** --Column headers for both Cycles 1 and 2: Treatment Course (two courses per cycle) were deleted. --Column headers for Day 1 and Day 15 ± 3 days had parenthetical information deleted --Column header: End of Treatment, cross-reference to previous footnote "j" about radiographic imaging was deleted and cross-reference to footnote "m" was revised to footnote "j" which reads: EOT assessments should be conducted within 28 days (± 5 days) after the last dose of onvansertib is administered. Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival for 1 year after EOT, at which	--Clarifications --End of Study procedures became End of Treatment instead.

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			point they will be considered to have completed the study (EOS).	
51.	Table 6-1	**Table 6-1 Schedule of Assessments** N/A	**Table 6-1 Schedule of Assessments** --New footnote "a" added to existing row of Confirmation of all Eligibility criteria: Eligibility will be confirmed by submission of an eligibility checklist including de-identified supporting source documents to the CRO Medical Monitor for review and approval. Documentation of a KRAS mutation in exon 2, 3, or 4 as determined by an assay performed in a CLIA-certified laboratory must be provided for inclusion in the study.	Updates to procedures for confirmation of eligibility criteria. Note that already established requirement for documentation of KRAS mutation in exon 2, 3, or 4 in primary tumor or metastasis, assessed by a CLIA-certified laboratory was also added as a clarification to this footnote.
52.	Table 6-1	**Table 6-1 Schedule of Assessments** --Row of Liquid biopsy for KRAS test and corresponding footnote "a": Blood for KRAS liquid biopsy will be obtained at screening for Phase 2 only. Blood will be collected in two 10-mL CEE-Sure tubes (for overnight delivery to [redacted]	**Table 6-1 Schedule of Assessments** N/A	Deleted as liquid biopsies for KRAS mutation will not be performed and confirmation by liquid biopsy of KRAS mutation status is not required for study eligibility
53.	Table 6-1	**Table 6-1 Schedule of Assessments** --Row of Triplicate 12-lead ECG at screening and Day 1 of Cycles 2 and beyond	**Table 6-1 Schedule of Assessments** --Moved triplicate ECG assessments during study from Table 6-1 to new **Table 6-2 Schedule of Assessments for PK Sampling** and schedule revised to Days 1 and 5 for Cycles 1, 3, and 5, to coincide with PK sampling times with associated footnote "b" that reads as follows: 12-lead ECGs will be obtained to coincide with PK sampling times. All ECGs should be performed in triplicate. ECG will also be performed at Screening (see Table 6-1).	--Moved during treatment ECG assessments from Table 6-1 to new Table 6-2. Note that ECG at screening was retained in Table 6-1.
54.	Table 6-1	**Table 6-1 Schedule of Assessments** Footnote "e" for blood chemistry and CEA row and CBC with differential row: Blood	**Table 6-1 Schedule of Assessments** Footnote "f" for blood chemistry and CEA row and CBC with differential row: Blood	Added clarification for Day 8 schedule of assessments sampling.

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		chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. CBC and clinical chemistry testing (including CEA) may occur up to 48 hours prior to Day 1 and Day 15 (CBC) and Day 1 (clinical chemistry).	chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. CBC and clinical chemistry testing (including CEA) may occur up to 48 hours prior to Day 1 and Day 15 (CBC) and Day 1 (clinical chemistry). The Day 8 sample will be collected in Cycle 1 only and may occur up to 24 hours before or after Day 8.	
55.	Table 6-1 and Table 6-2	**Table 6-1 Schedule of Assessments** Had row for blood samples for PK assessment at Cycle 1, Days 5, 6, 7, and 8 with associated footnote "f " that read: Blood samples for PK analysis will be obtained during cycle 1, only, on Days 5, 6, 7, and 8. Samples on Day 5 should be collected pre-dose and 1, 2, 3, 4, and 8 hours post dose; samples on other days should be collected 24, 48, and 72 hours post-Day 5 dose, respectively.	**Table 6-1 Schedule of Assessments**, moved PK sampling times to new **Table 6-2 Schedule of Assessments for PK Sampling** and schedule revised to Days 1 and 5 for Cycles 1, 3, and 5, with corresponding footnote "a" that reads as follows: Blood samples for PK analysis will be obtained during C1D1, C1D5, C3D1, C3D5, C5D1 and C5D5. Samples on C1D1, C3D1, and C5D1 should be collected pre-dose, and samples collected on C1D5, C3D5, and C5D5 should be collected 2 to 4 hrs after the patient has taken the dose. --New **Table 6-2 Schedule of Assessments for PK Sampling** had food effect substudy blood sampling added on C3D5 and C5D5 with associated footnote "c" that reads as follows: See Section 6.2.11.4 for details. Note that the PK samples collected for the food effect study on C3D5 and C5D5 may overlap with those collected for general PK analysis (from 2 to 4 hours postdose). One blood sample can be used to satisfy both blood draw requirements.	PK sampling times revised and moved from Table 6-1 to new Table 6-2; new food effect substudy sampling times newly added to this table.

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56.	Table 6-1	**Table 6-1 Schedule of Assessments** --Row for archival tumor tissue at screening if available (not required) and corresponding footnote "g": Availability and access to archival tissue does not need to occur prior to enrollment. Archival tumor tissue can be obtained after accrual and stored for future analysis, with patient consent. --N/A for tumor tissue sample submission	**Table 6-1 Schedule of Assessments** --Row for archival tumor tissue and corresponding previous footnote "g" deleted. --New row added of Tumor tissue sample submission at Screening with new footnote "b": Tumor tissue (FFPE) will be collected at study entry for central confirmation of KRAS mutation status and future correlated biomarker studies. If archival FFPE tissue is not available, the patient must undergo a biopsy at screening to obtain tissue for eligibility. Confirmation of KRAS mutation in tumor samples is not required for study eligibility.	Patients must have FFPE tumor tissue (newly acquired or archival) in order to be eligible.
57.	Table 6-1	**Table 6-1 Schedule of Assessments** -Row for blood samples for ctDNA had blood collected at Days 1 and 7 of Cycle 1 and Day 1 of Cycles 2 and beyond. --Corresponding footnote "h": Blood for ctDNA assessment should be collected on Days 1 (pre-dose) and 7 of Cycle 1; on Day 1 of Cycles 2 to 9, and at EOS. Blood will be collected in three 10-mL Streck tubes (for overnight delivery to Trovagene).	**Table 6-1 Schedule of Assessments** --Row for blood samples for ctDNA has blood collected at Day 1 of Cycle 1 and again at Day 1 of Cycles 2 and 3 and every other Cycle after Cycle 3. --Corresponding footnote "g": Blood for ctDNA assessment should be collected predose on Day 1 of Cycles 1, 2, 3, and every other Cycle after Cycle 3 (Cycle 5, Cycle 7, Cycle 9, etc), and at EOT. Blood will be collected in three 10-mL Streck tubes (for overnight delivery to Cardiff Oncology).	Changed frequency of ctDNA collection and where delivered.
58.	Table 6-1	**Table 6-1 Schedule of Assessments** -Row for blood samples for circulating tumor cells (CTCs) at Day 1 and EOS. --Corresponding footnote" i": Blood for CTC assessment should be collected on Day 1 of Cycle 1 (pre-dose), and at EOS. At each time point, blood will be collected	**Table 6-1 Schedule of Assessments** N/A	Deleted collection of CTCs.

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		in one 10-mL Streck tube (for delivery overnight to [redacted]).		
59.	Table 6-1	**Table 6-1 Schedule of Assessments** --Row for Disease assessment (radiographic imaging) --Corresponding footnote "j": Radiographic imaging will be obtained during screening, prior to the start of Cycles 3, 5, 7 etc., until EOS, and at EOS. Radiographic imaging should include CT of the chest/abdomen/pelvis with contrast (or MRI if contraindication to intravenous contrast). Radiographic imaging may occur up to 28 days prior to the first dose of onvansertib (study drug). --Row for re-staging at Screening and at Cycles 2 and Beyond and corresponding footnote "l" that said Restaging with CT or MRI should be done at screening within 28 days of administering the first dose of onvansertib and prior to the start of Cycles 3, 5, 7 etc., until EOS.	**Table 6-1 Schedule of Assessments** --Revised Row to say Disease assessment (radiographic imaging) and re-staging --Corresponding footnote "h": Radiographic imaging will be obtained during screening, prior to the start of Cycle 3 and at 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. 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. Radiographic imaging should include CT of the chest/abdomen/pelvis with contrast (or MRI if contraindication to intravenous contrast). Radiographic imaging may occur up to 28 days prior to the first dose of onvansertib (study drug). --Previous row for re-staging and corresponding prior footnote "l" was deleted.	Requirements for radiographic imaging were revised and clarified.
60.	Table 6-1	**Table 6-1 Schedule of Assessments** Onvansertib footnote "k": Patients will take onvansertib on Days 1 through 5 of each 14-day treatment course. Onvansertib will be dosed in the clinic on Day 1 of each cycle, but otherwise may be taken at home for patient convenience.	**Table 6-1 Schedule of Assessments** Onvansertib footnote" i": Patients will take onvansertib on Days 1 to 5 and Days 15 to 19 of each 28-day treatment course. Onvansertib will be dosed in the clinic on Day 1 of each cycle, and Day 5 of Cycles 1, 3, and 5 but otherwise may be taken at home for patient convenience.	Clarification
61.	Section 6.2.3	**Section 6.2.3 Liquid Biopsy for KRAS Test**	**6.2.3 Confirmation of KRAS Mutation Status**	--Liquid biopsies for KRAS mutation will not be performed

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		In the Phase 2 segment of the trial, confirmation of a KRAS mutation will be obtained by liquid biopsy during screening to confirm eligibility.	Documentation of a KRAS mutation in exon 2, 3, or 4 as determined by an assay performed in a CLIA-certified laboratory must be provided for inclusion in the study.	and confirmation by liquid biopsy of KRAS mutation status is not required for study eligibility. --Note that already established requirement for documentation of KRAS mutation in exon 2, 3, or 4 in primary tumor or metastasis, assessed by a CLIA-certified laboratory replaced the prior text.
62.	Section 6.2.4	**Section 6.2.10 Archival Tumor Tissue** Availability and access to archival tumor tissue samples does not need to be confirmed by the site prior to enrollment in accordance with the Schedule of Assessments (Table 6 1). If available, archival tumor tissue can be obtained after accrual for future use. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 10 to 30 unstained slides of whole sections of representative tumor tissue are preferred. Where two 2 mm cores of tumor from the block are unavailable, 10 to 30 unstained slides of whole sections of representative tumor tissue alone are acceptable. Availability and consent for use of archival tumor tissue is not required for study eligibility.	**Section 6.2.10 on Archival Tissue Tumor-** deleted and **Section 6.2.4 called Tumor Sample Submission** added: For all patients enrolled under version 2.0 of the protocol, tumor tissue (FFPE) will be collected at study entry. If archival FFPE tissue is not available, the patient must undergo a biopsy to obtain tissue for eligibility. Note that confirmation of KRAS mutation status in the submitted tumor samples is not required for study eligibility. FFPE tumor tissue requirements: • Tumor sample requirements: o Specimens from the most recent biopsy procedure should be submitted, and must be less than six years old o Optimal tumor cross sectional size = 25 mm^2, minimum = 5 mm^2 o Tumor is required to be at least 20% of the sample by ratio of tumor nuclei to benign nuclei	Patients must have FFPE tumor tissue (newly acquired or archival) in order to be eligible.

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			• FFPE Fixation requirements o 10% formalin fixation (neutral buffered) for 6 to 72 hrs, paraffin embedded. o No decalcification of the samples (EDTA decalcification is accepted) • Submit either an FFPE block or unstained slides: o If submitting slides: provide a minimum of 10 unstained slides cut at 5 microns on positively charged, unbaked slides and 1 stained hematoxylin and eosin (H&E) slide. If an H&E slide is not available, provide 11 unstained slides. Submit 10 additional slides if tissue size is < 25mm^2. o If submitting an FFPE block: choose the block with greatest tumor content. At least one stained H&E slide is required, or an extra unstained slide cut from the block will be generated if H&E slide is not available.	
63.	Section 6.2.9	**Section 6.2.9 Electrocardiograms** Twelve-lead ECGs will be performed in triplicate in accordance with the Schedule of Assessments (Table 6-1). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. Any clinically significant changes in	**Section 6.2.10 Electrocardiograms** Twelve-lead ECGs will be performed in triplicate at Screening (Table 6-1) and in accordance with the Schedule of Assessments for Pharmacokinetic Sampling (Table 6-2). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to	--Added cross-reference to Table 6-2 as ECG assessments now appear on both Table 6-1 (ECG at screening) and Table 6-2 (ECG assessments during treatment).

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		ECGs that occur during the study should be reported as an AE in the eCRF.	prevent changes in heart rate. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF.	
64.	Section 6.2.11.2	**Section 6.2.11.2 Hematology** CBC may occur up to 48 hours prior to Days 1 and 15.	**Section 6.2.11.2 Hematology** Hematology testing: CBC may occur up to 48 hours prior to Days 1 and 15 and 24 hours prior to, or after, Day 8.	Revision to frequency of CBC testing.
65.	Section 6.2.11.3	**Section 6.2.11.3 Samples for Pharmacokinetic Analysis** Blood samples for PK analysis should be obtained during Cycle 1 only on Days 5, 6, 7, and 8 in accordance with the Schedule of Assessments (Table 6-1).	**Section 6.2.11.3 Samples for Pharmacokinetic Analysis** Pharmacokinetic samples were obtained from patients in the Phase 1b portion of the study to better characterize PK and allow for population PK and exposure-related analyses to facilitate onvansertib dose selection for the Phase 2 portion of the trial. PK samples will also be collected from all patients enrolled on the Phase 2 portion of the study under version 2.0 of the protocol for further exposure-related analyses of the 15 mg/m^2 dose according to the Schedule of Assessments for PK sampling (Table 6-2). Triplicate ECGs should be obtained as close as possible to the PK blood sampling.	--Cross-reference to newly added Table 6-2, Schedule of Assessments for PK Sampling. --PK sampling times revised and moved from Table 6-1 to new Table 6-2; food effect substudy sampling times newly added to this table. --Added that ECGs should be obtained as close as possible to the PK blood sampling.
66.	Section 6.2.11.4	N/A	**Section 6.2.11.4 Food Effect Substudy** A subgroup of patients (at least 12 patients) enrolled on the Phase 2 portion of the study will participate in a preliminary food effect study. The food effect study will be conducted during Cycles 3 and 5 for the participating patients. All patients should come to the clinic after an overnight fast, and be provided with either water or a fat-containing meal. This substudy will follow a cross-over design, with half of the participating patients (at least 6) taking their onvansertib dose on C3D5 in clinic in a	Section added for new food effect substudy

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			fasted state, with water only. On C5D5, these patients will take their dose 30 minutes after the consumption of a fat-containing meal. PK samples will be drawn immediately before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 24 hours post-dose following both the fasted dose on C3D5 and the fed dose on C5D5 (also see Table 6-2). The second half of the food effect study participants (at least 6 patients) will undergo the same testing on Cycles 3 and 5, but the order of the fasted and fed states will be reversed; ie, the second group will take their onvansertib dose in a fed state on C3D5 and will take their dose in a fasted state on C5D5.	
67.	N/A	**Section 6.2.11.4 Samples for Circulating Tumor Cell Assessment** Blood for CTC assessment should be collected prior to study treatment administration on Cycle 1 Day 1 and at EOS, as outlined in the Schedule of Assessments (Table 6-1). At each time point, blood will be collected in one 10-mL Streck tube (for overnight delivery to [redacted]).	N/A	Deleted collection of CTCs.
68.	Section 6.2.12	**6.2.12 Disease Assessment: Radiographic Imaging** Radiographic imaging using RECIST v1.1 will be obtained prior to the start of Cycle 3 and all subsequent odd numbered cycles and at EOS, as outlined in Schedule of Assessments (Table 6-1). Radiographic imaging may occur up to 28 days prior to administration of the first dose of onvansertib (study drug).	**6.2.12 Disease Assessment: Radiographic Imaging** Baseline radiographic imaging may occur up to 28 days prior to administration of the first dose of onvansertib (study drug). CT is the preferred modality, but MRI is acceptable. The same imaging modality should be used throughout the trial. Radiographic imaging for disease restaging during the treatment period will be obtained at screening, prior to the start of Cycle 3	Requirements for radiographic imaging were revised and clarified.

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		Restaging with CT or MRI should be done within 28 days of the first dose of onvansertib and prior to the start of Cycle 3 and all subsequent odd numbered cycles, until EOS.	and at 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 (Table 6-1). Patients who are taken off onvansertib, but remain on FOLFIRI + bevacizumab or any component(s) of the FOLFIRI + bevacizumab regimen are not considered to have started a new anti-cancer therapy and should continue to undergo scans every 8 weeks. Radiographic imaging should include CT of the chest/abdomen/pelvis with contrast (or MRI if the patient has contraindication to intravenous contrast).	
69.	Section 6.2.13	**Section 6.2.13 End-of-Study/Follow-Up** The EOS visit should occur within 28 days after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1). Follow-up information will be collected via voice or written contact approximately every 8 weeks until PD (from patients with SD or better) at the end of treatment assessments.	**Section 6.2.13 End of Treatment/Follow-Up/End of Study** The EOT visit should occur within 28 days (± 5 days) after the last dose of onvansertib is administered, and should include the assessments outlined in the Schedule of Assessments (Table 6-1). Patients (any ongoing from Phase 1b and all from Phase 2) will be followed for overall survival for 1 year after EOT. Follow-up information regarding post-study treatment, including duration of treatment, will be collected approximately every 8 weeks during this 1-year period. Once 1 year of follow-up after EOT has been completed, the patient will be considered to have completed the study (EOS).	--EOS visit changed to EOT visit --Revised follow-up for Phase 2.
70.	Section 7.3	**Section 7.3 Relationship of Adverse Events to the Study Drug** The Investigator must attempt to determine if an AE is in some way related to the use of the onvansertib. All AEs must be	**Section 7.3 Relationship of Adverse Events to the Study Drug** The Investigator must attempt to determine if an AE is in some way related to the use of	Deleted requirement that all AEs must be attributed to study drug unless there is a reasonably acceptable alternate cause for the AEs.

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		attributed to study drug unless there is a reasonably acceptable alternate cause for the AEs. This relationship should be described as follows:…	onvansertib. This causal relationship should be described as follows:…	
71.	Sections 8, 8.1 and 8.2	**Section 8: PATIENT DISCONTINUATION AND TRIAL DISCONTINUATION** **Section 8.1 Patient Discontinuation** A patient may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled… Patients who are discontinued prior to completing the first treatment cycle (28 days; there are two 14-day courses of treatment in each 28-day cycle) for any reason other than toxicity, or who have not received at least 80% of the intended doses, will be replaced. **Section 8.2 Study Discontinuation:** If 2 or more DLTs are observed in a 3-patient or 6-patient cohort at a given dose level and no lower dose for de-escalation exists, the study will be stopped and subjects and investigators will be notified of termination of the study.	**Section 8: PATIENT TREATMENT AND STUDY DISCONTINUATION AND SPONSOR TRIAL DISCONTINUATION** **Section 8.1 Patient Discontinuation** A patient may choose to stop treatment and/or withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled… Patients enrolled in the completed Phase 1b portion of the study who discontinued from treatment prior to completing the first treatment cycle (28 days) for any reason other than toxicity, or who did not receive at least 80% of the intended doses, may have been replaced. **Section 8.2 Study Discontinuation:** In the completed Phase 1b portion of the study, if 2 or more DLTs were observed in a 3-patient or 6-patient cohort at a given dose level and no lower dose for de-escalation existed, the study would have been stopped and patients and the Investigators would have been notified of termination of the study.	--Clarified patient discontinuation to also mean patient choosing to stop treatment. --Clarified replacement of subjects in Phase 1b. --Clarified that DLTs were evaluated in the completed Phase 1b portion of the study.
72.	Section 9.1	**Section 9.1 Determination of Sample Size** This is a single-arm study that consists of determining the MTD and RP2D in the Phase 1b segment of the trial, and using the RP2D to treat patients in the Phase 2 continuation segment.	**Section 9.1 Determination of Sample Size** 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	Sample size revisions for Phase 2.

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			of the study has been amended to enroll additional patients at 15 mg/m^2 to obtain additional PK, PD, 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).	
73.	Section 9.1.1	**Section 9.1 Determination of Sample Size** **Section 9.1.1 Phase 1** A standard 3 + 3 dose-escalation design will be used (Le Tourneau 2012) as described in in Section 3.1.2. The dose escalation scheme and DLT evaluation plan is outlined in Section 3.1.2.1. Patients will be enrolled to one of the series of doses levels shown in Table 5-1 (onvansertib) and Table 5-2 (FOLFIRI and bevacizumab). Enrollment in Phase 1b will stop when 6 patients have been treated at the highest dose level at which 1 or fewer patients experience a DLT. The number of patients to be enrolled in Phase 1b depends on the observed safety profile, which will determine the number of patients enrolled in each cohort. The total number of patients is expected to be up to 18 (up to 6 patients per cohort).	**Section 9.1 Determination of Sample Size** **Section 9.1.1 Phase 1b** A standard 3 + 3 dose-escalation design was used (Le Tourneau 2012) as described in Section 3.1.2. The dose escalation scheme and DLT evaluation plan used is outlined in Section 3.1.2.1. 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 (up to 6 patients per cohort).	Revisions reflect completion of Phase 1b.
74.	Section 9.1.2	**Section 9.1 Determination of Sample Size** **Section 9.1.2 Phase 2** In Phase 2, patients will be enrolled and treated at the RP2D of onvansertib. The definition of the RP2D is provided in Section 3.1.3.1. The group of up to 6 patients who were enrolled at what was	**Section 9.1 Determination of Sample Size** **Section 9.1.2 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) of onvansertib on Days 1 to 5 and 15 to 19 of a 28 day cycle concurrently with FOLFIRI +	--The group of 6 patients enrolled at 15 mg/m^2 in Phase 1b will not be used in the primary analytic cohort for Phase 2, but will be used in selected analyses. --Null hypothesis adjusted.

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		determined to be the the (sic) RP2D in Phase 1b will be included in the analytic cohort for Phase 2. Final determination of the RP2D will be based on evaluating all available data from the dose escalation Phase 1b portion of the trial, including low-grade, but chronic toxicities, dose reductions and/or missed doses of onvansertib. Assuming 12 months of accrual during Phase 2 at 26 patients per year, resulting in 26 total patients, and with 6 months follow-up on the last patient enrolled, and based on a one-sided one sample log-rank test with 10% Type I error, there will be at least 90% power to detect an improvement in ORR from 5% to 20%. This sample size assumes a drop out of 10%. The primary endpoint for Phase 2 will be ORR. Response rate will be compared with an historical baseline of 5% based on based on the reported results of bevacizumab treatment in second-line setting (Bennouna 2013). The expected response rate is 20%, to reflect a significant improvement over other currently approved antiangiogenic agents (ziv-aflibercept and ramucirumab), with response rates of 12 to 15%. Using Southwest Oncology Group's (SWOG's) one-arm binomial calculator, with 10% Type I error and 90% power, 29 patients are needed for the Phase 2 portion. The group of up to 6 patients who were enrolled at what is determined to be the RP2D in Phase 1b will be included in the analytic cohort for Phase 2.	bevacizumab. The definition of the RP2D is provided in Section 3.1.3.1. 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. Selection of 15 mg/m^2 as 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 the study, 15 mg/m^2 was chosen as the RP2D. 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%.	--Plan is to include approximately 80 rather than 26 evaluable patients. --Power revised.

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		Assuming a dropout rate of 10%, the plan is to include a total of 26 new patients in the Phase 2 portion of the study.		
75.	Section 9.3.1	**Section 9.3 Statistical Analysis** **Section 9.3.1 Statistical Analysis of Safety Data** Data from all patients who receive at least 1 dose of study drug (onvansertib) will be included in the safety analysis…	**Section 9.3 Statistical Analysis** **Section 9.3.1 Statistical Analysis of Safety Data** Data from all patients who receive at least 1 dose of any study drug will be included in the safety analysis…. Other safety assessments will include data from concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, ECG measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (e.g., mean, median, range, and standard deviation for continuous data; and frequency for categorical data).	--Revised analysis of safety data to include those who receive at least 1 dose of any study drug rather than 1 dose of onvansertib. --Added paragraph on other safety assessments for safety analysis...
76.	Section 9.3.2.1	**Section 9.3.2 Statistical Analysis for Phase 2** **Section 9.3.2.1 Primary Analysis** The primary endpoint for Phase 2 will be response rate. Response rate will be compared with an historical baseline of 5% based on based on the reported results of bevacizumab treatment in second-line setting (Bennouna 2013). The expected response rate is 20%, to reflect a significant improvement over other currently approved antiangiogenic agents (ziv-aflibercept and ramucirumab). Response rate is defined as a CR or PR according to Investigator's assessment using RECIST v1.1 from the first dose of study treatment until PD or death due to any cause. Patients with inadequate data for	**Section 9.3.2 Statistical Analysis for Phase 2** **Section 9.3.2.1 Primary Analysis** The primary endpoint for Phase 2 will be objective response rate (ORR). Response rate will be compared with a historical baseline of 15% based on the reported results of FOLFIRI-bevacizumab treatment in second-line setting (Antoniotti 2020; Cremolini 2020). The expected response rate is 30% to reflect a clinically meaningful endpoint for this population with limited treatment options and with presumed limited activity of currently available regimens. Response rate is defined as a CR or PR according to Investigator's assessment of radiographic imaging results using RECIST	Primary analyses revised.

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		tumor assessment (e.g., no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of response rate.	v1.1. Patients with missing or unknown response information will be classified as non-responders. Patients from Phase 2 who receive at least 1 cycle (28 days/4 weeks of treatment) of onvansertib (treated-patient population) will be included in the treated-patient population for efficacy analysis. Patients who have radiographically-confirmed PD prior to the completion of the first cycle will be excluded from this analysis. The percentage of patients who experience a CR or PR based on RECIST v1.1 will be presented, along with the associated 95% confidence interval.	
77.	Section 9.3.2.2	**Section 9.3.2 Statistical Analysis for Phase 2** **Section 9.3.2.2 Analysis of Secondary Endpoints** PFS is defined from the start of treatment to the first observation of PD or death, whichever comes first. The patients who are alive and PD is not observed, PFS will be censored at the date of the latest disease assessment.	**Section 9.3.2 Statistical Analysis for Phase 2** **9.3.2.2 Analysis of Secondary Endpoints** All secondary efficacy endpoint analysis will be carried out in the treated-patient population (ie, all patients receiving at least 1 cycle of onvansertib). Patients who have radiographically-confirmed PD prior to the completion of the first cycle will be excluded from these analyses. PFS is defined from the start of treatment to the first observation of PD or death, whichever comes first. The patients who are alive and PD is not observed, PFS will be censored at the date of the latest disease assessment. DOR is defined from the date of first response (CR or PR) to PD or death, whichever occurs first. This endpoint will be evaluated only in patients who have objective response of CR or PR.	Secondary analyses expanded.

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			DCR is defined as the number of patients achieving SD, PR, or CR. Overall survival will be calculated for 1 year following EOT, at which point the patients will be considered to have completed the study (EOS). Blood samples obtained at baseline and subsequent time points as indicated in the Schedule of Assessments (Table 6-1) will be analyzed for the presence of ctDNA (including KRAS mutations) to assess changes in KRAS allelic burden. Summary statistics of PK parameters will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided. Log-transformation of exposure measurements may be conducted as needed.	
78.	Section 9.3.3	**Section 9.3.2 Statistical Analysis for Phase 2** **Section 9.3.2.3: Analysis of Exploratory Endpoints** **Section 9.3.2.3.1: Reduction in KRAS Allelic Burden on Liquid Biopsies** Blood samples obtained at baseline and subsequent time points as indicated in the Schedule of Assessments (Table 6-1) will be analyzed for the presence of ctDNA (including KRAS mutations). **Section 9.3.3 Statistical Analysis of Pharmacodynamic Data** Circulating tumor cells and circulating tumor DNA isolated from blood samples will be used to assess inhibition of PLK1 activity by onvansertib and to evaluate	**Section 9.3.3 Analysis of Pharmacodynamic and Pharmacokinetic Data (Exploratory Endpoints)** ctDNA isolated from blood samples will be used to monitor changes in KRAS MAF and to evaluate relevant biomarkers correlated with patient response in the treated-patient population. 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 pharmacodynamic analysis will include assessments of pharmacodynamic biomarkers in both blood and tumor tissue. The relationship between onvansertib	Statistical analysis for exploratory endpoints revised and expanded, including for new food effect substudy.

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		relevant biomarkers correlated with patient response. If available and consent is given by the subject, archival tumor tissue may be used to evaluate genomic profiles (DNA/RNA) associated with patient response.	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 pharmacodynamic analyses may be conducted as appropriate. To evaluate the impact of concomitant food intake, descriptive statistics of PK parameters, by fed and fasted state, along with the ratio of geometric means between fed and fasted states will be provided. Summary statistics related to this examination will include, but is not necessarily limited to: C_{max}, T_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. Averages, standard deviations, and coefficients of variation will be provided. Log-transformation of exposure measurements may be conducted as needed for PK and pharmacodynamic associated analyses.	
79.	Section 15	**Section 15 Reference**s N/A	**Section 15 Reference**s Antoniotti C, Cremolini C, Rossini D, et al. TRIBE2 results and toxicity - Authors' reply. Lancet Oncol 2020;21:e300-1. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet	New reference citations added.

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			Oncol 2020;21:497-507. Hong DS, Fakih MG, Strickler JH, et al. KRAS(G12C) inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-1217.	