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Protocol for Study M14-064

Metastatic Colorectal Cancer: ABT-165 plus FOLFIRI vs Bevacizumab plus FOLFIRI in Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidine, Oxaliplatin and Bevacizumab

VERSION:	3.0	DATE:	07 February 2019
SPONSOR:	AbbVie Inc.	NUMBER OF SITES:	Up to 60
ABBVIE INVESTIGATIONAL PRODUCT:	ABT-165	EUDRACT:	2017-003669-87

FULL TITLE: Phase 2 Study Comparing Efficacy and Safety of ABT-165 plus FOLFIRI vs Bevacizumab plus FOLFIRI in Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidine, Oxaliplatin and Bevacizumab

Incorporating Versions 1.0, 2.0, and 3.0.

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1 SYNOPSIS

Title: Phase 2 Study Comparing Efficacy and Safety of ABT-165 plus FOLFIRI vs Bevacizumab plus FOLFIRI in Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidine, Oxaliplatin and Bevacizumab	
Background and Rationale:	ABT-165 inhibits both vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4). Combined blockade of VEGF and DLL4 is more efficacious than blockade of VEGF alone for inhibition of subcutaneous xenograft growth of human tumor cell lines derived from colon, breast, and glioblastoma in animal studies. The combination of ABT-165 plus FOLFIRI is hypothesized to prolong progression-free survival (PFS) in second-line metastatic colorectal cancer (mCRC) subjects more than the combination of bevacizumab plus FOLFIRI while demonstrating similar safety and tolerability.
Objective(s) and Endpoint(s):	Primary objective: • To estimate PFS, as determined by blinded independent central review, of ABT-165 plus irinotecan, fluorouracil (5-FU) and leucovorin (folinic acid) chemotherapy regimen (FOLFIRI) compared to bevacizumab plus FOLFIRI in subjects with previously treated mCRC who have received a regimen containing a fluoropyrimidine, oxaliplatin, and bevacizumab. Secondary objective: • To assess overall survival (OS), objective response rate (ORR), safety, and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI. Exploratory objectives: • To evaluate predictive biomarkers for association with efficacy and safety. • To correlate DLL4 expression level with response (PFS, OS, and ORR). • To evaluate the pharmacodynamic effect between the 2 treatment groups to establish engagement of DLL-4 in the ABT-165 arm. • To explore safety-exposure and efficacy-exposure relationship in the ABT-165 treatment arm. Primary endpoint: • The primary endpoint is PFS. PFS will be defined as the time from randomization until the first occurrence of radiographic progression, as determined by blinded independent central review, or of death from any cause. PFS time for a subject who does not have a PFS event will be censored at the time of the last tumor assessment. Secondary endpoints: • Overall Survival (OS): OS is defined as the time from randomization until death from any cause. Duration of

	survival for subjects who are still alive at the time of analysis will be censored on the date of last contact. • Objective Response Rate (ORR): ORR will be defined as the proportion of subjects with a complete response (CR) or partial response (PR) as determined by blinded independent central review based on RECIST, Version 1.1. Safety endpoints: • Safety and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI will be assessed. • Safety evaluations include study drug exposure, adverse event (AE) monitoring, serious adverse event (SAE) monitoring, recording of all deaths, clinical laboratory testing, and vital sign assessments as measures of safety and tolerability for the entire study duration.
Investigator(s):	Multi-center
Study Site(s):	Up to 60 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 100 adult subjects with a histologically or cytologically confirmed diagnosis of metastatic adenocarcinoma of the colon or rectum who have progressed following a fluoropyrimidine/oxaliplatin/bevacizumab-regimen
Investigational Plan:	Open-label, randomized, multi-center, treatment-controlled study to evaluate the efficacy and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI in subjects with previously treated metastatic adenocarcinoma of the colon or rectum, whose primary tumor has been resected. Subjects will be randomized in a 1:1 ratio to ABT-165 plus FOLFIRI or bevacizumab plus FOLFIRI. Subjects in either arm will receive FOLFIRI as irinotecan, leucovorin, 5-FU bolus immediately followed by 5-FU infusion on Day 1 of each 14-day cycle in addition to ABT-165 or bevacizumab.
Key Eligibility Criteria:	• Diagnosis of histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum. • At least 1 lesion on a computed tomography (CT) scan that is measurable as defined by RECIST, Version 1.1. • Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. • Progression following treatment with fluoropyrimidine/oxaliplatin/bevacizumab-regimen in the metastatic setting. • Adequate hematologic, renal, and hepatic function. • Lack of clinically significant conditions which increase the risk for antiangiogenic therapy, including presence of intact primary tumor.

Study Drug and Duration of Treatment:	ABT-165, 2.5 mg/kg (or 1.25 mg/kg for the first 2 cycles), plus FOLFIRI (irinotecan 180 mg/m^2, leucovorin DL-400 mg/m^2 or L-200 mg/m^2, fluorouracil bolus: 400 mg/m^2, then continuous infusion: 1200 mg/m^2/day × 2 days - total of 2400 mg/m^2 over 46 – 48 hours) intravenously on Day 1 of each 14-day cycle or bevacizumab, 5 mg/kg, plus FOLFIRI intravenously on Day 1 of each 14-day cycle The FOLFIRI dosing may be modified based on Investigator judgment and institutional standards. For both treatment arms, the first infusion will be administered over 60 (± 10) minutes. If the first infusion is tolerated, the second infusion and subsequent infusions will be administered over 30 (± 10) minutes as tolerated.
Date of Protocol Synopsis:	07 February 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Preclinical evidence suggests that a combined blockade of delta-like ligand 4 (DLL4) and vascular endothelial growth factor (VEGF), resulting in a potent inhibition of DLL4 mediated Notch-1 activation and inhibition of VEGF-stimulated endothelial cell proliferation, could be a promising approach for the treatment of subjects with solid, metastatic neoplastic lesions, including metastatic colorectal cancer (mCRC). Current treatment paradigms for mCRC suggest that new treatments are needed to overcome intrinsic and acquired resistance against existing anti-VEGF therapies. AbbVie is developing a first-in class humanized recombinant DVD-Ig molecule with a dual specificity for human DLL4 and VEGF, ABT-165, which may address the current needs for subjects with mCRC.

ABT-165 binds with nanomolar affinities to DLL4 and VEGF, and blocks DLL4 and VEGF interaction with their cognate receptors; this results in potent inhibition of DLL4 mediated Notch-1 activation, and inhibition of VEGF-stimulated endothelial cell proliferation. In preclinical animal studies, combined blockade of both DLL4 and VEGF results in increased inhibition of subcutaneous (SC) xenograft growth of human tumor cell lines derived from colon, breast, and glioblastoma, relative to blocking either axis alone.[1,2] ABT-165 also induces tumor regression in vivo in combination with chemotherapy, with significantly better efficacy in comparison to anti-VEGF monoclonal antibody (mAb) treatment with cytotoxic agents.

Current standard second-line therapy for patients with mCRC includes FOLFIRI (irinotecan/fluorouracil [-FU]/leucovorin [Folinic Acid] with bolus and continuous infusion 5-FU). Fluorouracil (5-FU) is commonly administered with leucovorin, which modulates 5-FU activity. Irinotecan is active in advanced colorectal cancer (CRC) and was first approved by the Food and Drug Administration for patients with disease refractory to 5-FU/leucovorin. Initial approval was based on a response rate of about 15% and subsequently confirmed with a randomized study demonstrating improved survival for patients refractory to 5-FU who were treated with irinotecan compared to best supportive care.[3] Two combinations of irinotecan/5-FU/leucovorin were compared to 5-FU/leucovorin regimens, 1 with bolus 5-FU/leucovorin and another with continuous infusion 5-FU.[4,5] In both studies, the irinotecan-containing combinations conferred a survival advantage.

Three biological agents, and 1 biosimilar agent, targeting the VEGF-pathway have now been approved in second-line CRC in combination with FOLFIRI; bevacizumab, ziv-aflibercept, ramucirumab, and a bevacizumab biosimilar. Bevacizumab (Avastin) and bevacizumab biosimilar (MVASI) are both a recombinant humanized version of a murine anti-human VEGF mAb that has been clinically evaluated both as a single agent and in combination with cytotoxic chemotherapy in multiple metastatic solid tumor types. It is approved for use in the first- and second-line setting for advanced CRC in combination with fluorouracil-based chemotherapy.[6] In a study comparing irinotecan/5-FU/leucovorin with irinotecan/5-FU/leucovorin plus bevacizumab in first-line mCRC, a survival advantage of more than 4 months was observed in bevacizumab-treated patients.[7] In the BICC-C Phase 3 study of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line mCRC by Fuchs and colleagues, progression-free

survival (PFS) and overall survival (OS) were improved in bevacizumab combination versus respective chemotherapy only arms.[8] With the addition of bevacizumab to FOLFIRI, PFS improved from 7.6 to 11.2 months and OS from 23.1 to 28 months.[8] Bevacizumab does not appear to alter the toxicity profile of chemotherapy, although hypertension and proteinuria are commonly seen. Approximately 3.4% of patients receiving bevacizumab suffer arterial thrombotic events.

In patients who were previously treated with FOLFOX (leucovorin/fluorouracil/oxaliplatin) and bevacizumab in first-line therapy, the combination of FOLFIRI/bevacizumab increased median OS from 9.8 months to 11.2 months, an improvement of 1.4 months (Hazard Ratio [HR] = 0.81; $P < 0.0062$).[9] Similarly, another agent which binds to VEGF, ziv aflibercept, has been approved in second-line CRC in combination with FOLFIRI.[10] Aflibercept improved median OS (mOS) from 12.1 months to 13.5 months (an improvement of 1.4 months; HR = 0.817; $P < 0.0032$) in patients who had been previously treated with oxaliplatin-based regimens in first-line therapy.[11]

An antibody targeting the VEGF receptor (ramucirumab) has also been approved in combination with FOLFIRI in second-line CRC.[12] The combination of FOLFIRI and ramucirumab improved mOS from 11.7 to 13.3 months (an improvement of 1.6 months; HR = 0.85; $P = 0.023$) in patients who had previously been treated with oxaliplatin/bevacizumab-based regimens in first-line therapy. VEGF pathway-targeting agents provide a small yet statistically significant improvement in mOS but clearly agents that provide a greater benefit would be preferred.

Clinical Hypothesis

It is hypothesized that the combination of ABT-165 plus FOLFIRI will prolong PFS in second-line mCRC subjects more than the combination of bevacizumab plus FOLFIRI while demonstrating similar safety and tolerability.

2.2 Benefits and Risks to Patients

This study proposes to determine if subjects with second-line mCRC have improved PFS through the addition of ABT-165 to FOLFIRI chemotherapy compared to bevacizumab plus FOLFIRI. Preclinical data demonstrate that ABT-165 potentiates the anti-tumor activity of irinotecan and in clinical studies the combination of ABT-165 plus FOLFIRI appeared safe and tolerable. The current study is the first study to test whether subjects with CRC receiving ABT-165 have improved PFS compared to those receiving bevacizumab plus FOLFIRI.

Risks in this study include toxicity from the addition of ABT-165 to standard therapy. Preliminary safety data from a Phase 1 study of the proposed combination suggest a toxicity profile similar to that of bevacizumab plus FOLFIRI with potentially higher rates of hypertension and pulmonary hypertension. Since gastrointestinal perforation has occurred in subjects treated with ABT-165 on both the Phase 1/1b study and the current Phase 2 M14-064, additional exclusion criteria have been implemented in order to decrease the risk of this adverse event (AE) which can occur with VEGF inhibition. Furthermore, additional stopping rules based upon toxicity have been implemented.

For further details, please see the ABT-165 Investigator Brochure.[13]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

1. To estimate the PFS of ABT-165 plus irinotecan, fluorouracil and leucovorin chemotherapy regimen (FOLFIRI) compared to bevacizumab plus FOLFIRI, as assessed by blinded independent central review, in subjects with previously treated mCRC who have received a regimen containing fluoropyrimidine, oxaliplatin, and bevacizumab.

Secondary

2. To assess OS, objective response rate (ORR), safety, and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI.

Exploratory

1. To evaluate predictive biomarkers for association with efficacy and safety.
2. To correlate DLL4 expression level with response (PFS, OS, and ORR).
3. To evaluate the pharmacodynamic effect between the 2 treatment groups to establish engagement of DLL-4 in the ABT-165 arm.
4. To explore safety-exposure and efficacy-exposure relationship in the ABT-165 treatment arm.

3.2 Primary Endpoint

The primary endpoint is PFS. PFS will be defined as the time from randomization until the first occurrence of radiographic progression determined by blinded independent central review or until death from any cause. PFS time for a subject who does not have a PFS event will be censored at the time of the last tumor assessment.

3.3 Secondary Endpoints

Secondary Endpoints

1. Overall Survival (OS): OS is defined as the time from randomization until death from any cause. Duration of survival for subjects who are still alive at the time of analysis will be censored on the date of last contact.
2. Objective Response Rate (ORR): ORR will be defined as the proportion of subjects with a complete response (CR) or partial response (PR) as determined by blinded independent central review based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.

3.4 Safety Endpoints

Safety and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI will be assessed.

Safety evaluations include study drug exposure, AE monitoring, serious adverse event (SAE) monitoring, recording of all deaths, clinical laboratory testing, and vital sign assessments as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

Serum ABT-165 concentrations will be obtained at the visits as indicated in Appendix D and in Table 1 of the operations manual (Appendix F). Serum concentrations of ABT-165, the presence of anti-drug antibodies (ADA) and, as needed, the neutralization effect of the ADA (nAb) will be determined.

Serum concentration, ADA (if applicable), and if available nAb data from this study may be combined with data from other studies and analyzed using population pharmacokinetic (PK) methodologies.

3.6 Biomarker Research Endpoints

Samples may be collected to conduct exploratory investigations into known and novel biomarkers. Some of these samples will be optional. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids, or metabolites. Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of defining the relationship between biomarker levels and response. This research may be exploratory in nature and the results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are listed in Appendix D and the Operations Manual (Appendix F), Section 3.5.

Blood samples collected may be used to assess the effects of ABT-165, including but not limited to characterization of gene mutational status or expression of genes, particularly those involved in VEGF- and Notch-related signaling pathways. Markers of functional drug exposure such as soluble VEGF, and tumor response markers such as carcinoembryonic antigen may be explored in plasma as surrogates of drug responsiveness. Additional analyses may be performed as relevant and associated with response.

Examination of the plasma components of subjects on the ABT-165 clinical trials may reveal patterns of cell-free nucleic acids or protein/peptide concentrations that may be further evaluated in future clinical studies to determine any prognostic value and any correlation with clinical response. If warranted, circulating tumor-derived nucleic acids may be extracted from plasma and quantitated and/or assessed for methylation and mutational status of genes relevant to ABT-165 mechanism of action.

Archival Tissue and Fresh Biopsy Samples

Tissue slides from biopsies may be used to assess molecular characteristics and/or expression of protein, nucleic acids, metabolites, and presence of stromal cells such as lymphocytes. Additionally, these samples may be examined for mutations and/or methylation of nucleic acids. Analysis of relevant proteins, including but not limited to DLL4 expression, cancer stem cell marker expression, and/or expression of DLL4 downstream pathway genes, may be performed on tumor tissue obtained from each

consented subject when feasible. These analyses might reveal putative stratification and/or resistance markers for correlation with efficacy. If tumor tissue and plasma are available from the same subject, the results of studies may be compared to assess correlation of the methodologies.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F).

This is an open-label, randomized, treatment-controlled study to evaluate the efficacy and tolerability of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI in previously treated metastatic adenocarcinoma of the colon or rectum, whose primary tumor has been resected. Subjects will be randomized to 1 of 2 therapy groups as follows:

a. ABT-165 plus FOLFIRI

b. Bevacizumab plus FOLFIRI

Randomization will be stratified according to the subjects' RAS mutation status (mutation in K-RAS or N-RAS exons 2 – 4, yes versus no) and tumor location (right-sided including transverse colon to splenic flexure versus left-sided).

For the purposes of this study, protocol therapy will be defined as ABT-165 plus FOLFIRI. Control therapy will be defined as bevacizumab plus FOLFIRI. One cycle of therapy consists of 14 days. Subjects randomized to either arm will receive FOLFIRI as irinotecan, leucovorin, 5-FU bolus immediately followed by 5-FU infusion on Day 1 of each 14-day cycle. At the discretion of the Investigator, the 5-FU bolus or continuous infusion may be reduced or eliminated depending on the subject's tolerability of prior treatment. Subjects should continue to follow the dosing schedule for protocol therapy until disease progression or intolerable toxicity. Subjects who are not able to tolerate the FOLFIRI portion of the therapy may continue on either ABT-165 or bevacizumab alone until progression or intolerable toxicity. Subjects unable to tolerate ABT-165 or bevacizumab may continue on FOLFIRI or 5-FU alone until progression or intolerable toxicity. Subjects who have discontinued all study therapy due to intolerable toxicity should continue to undergo scheduled tumor assessments until radiographic progression is documented.

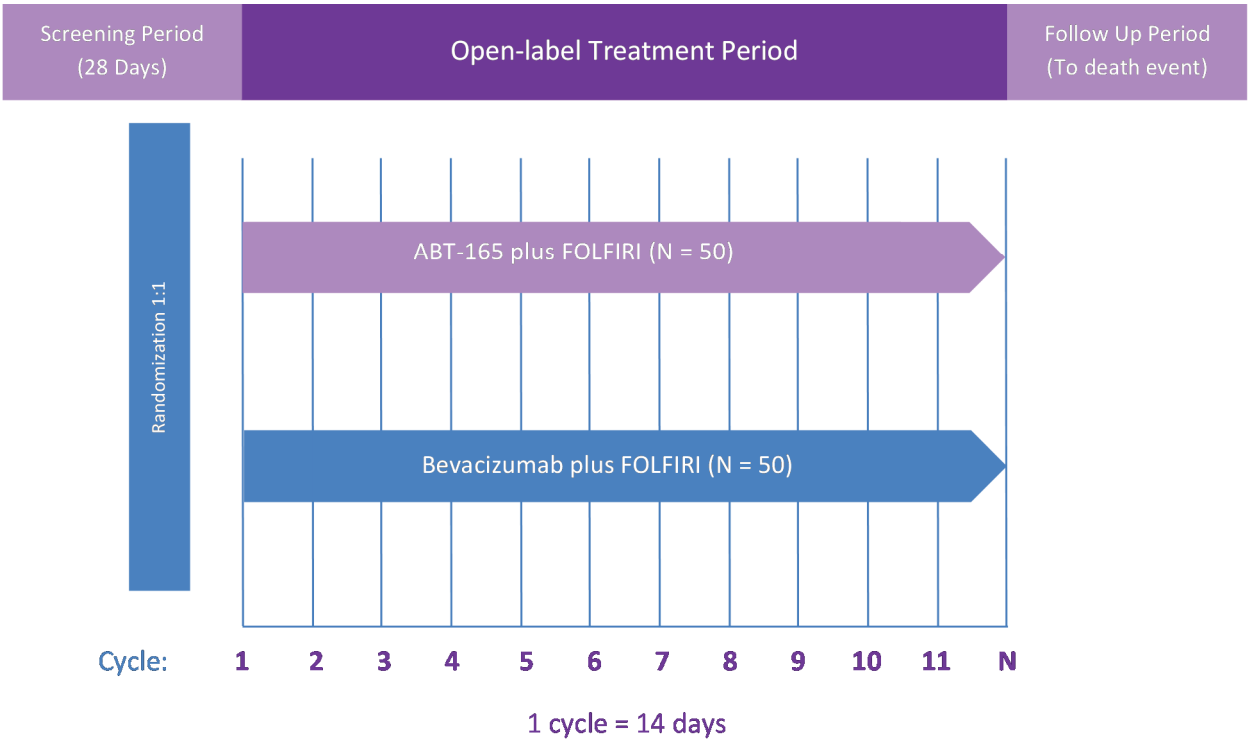
The study population will consist of subjects with metastatic adenocarcinoma of the colon or rectum who have progressed during or after 1 line of prior chemotherapy for their mCRC including fluoropyrimidine, oxaliplatin, and bevacizumab, but not irinotecan. See Section 5.1 for information regarding eligibility criteria.

Safety data will be monitored by the Sponsor and documented internally. Throughout study conduct for Study M14-064, individual subject safety data and aggregate safety data will be reviewed by the Safety Management Team, the Therapeutic Area Medical Director and the Product Safety Team Therapeutic Area Physician with potential safety signals assessed by a cross functional ABT-165 Product Safety Team. As part of routine pharmacovigilance, individual case safety reports are reviewed per timelines for

regulatory reporting and aggregate safety data reviewed on a quarterly basis by the previously referenced AbbVie personnel. Sites will be informed of any significant findings impacting subject safety as they arise.

An administrative interim analysis (AIA) for safety and efficacy will be conducted by an internal Data Monitoring Committee (DMC) after approximately 100 subjects are enrolled. The purpose of the AIA is to enable further development activities.

Figure 1. Study Design



4.2 Discussion of Study Design

Choice of Control Group

The control group will receive standard of care FOLFIRI plus bevacizumab, which is approved for second-line CRC subjects who previously progressed on a fluoropyrimidine/oxaliplatin/bevacizumab-regimen.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with mCRC. All clinical and laboratory procedures in this study are standard and generally accepted. Echocardiograms (ECHO) will be performed for safety to monitor for potential decrease in ejection fraction or pulmonary hypertension.

Suitability of Subject Population

Subjects with pathologically metastatic adenocarcinoma of the colon or rectum whose primary tumor has been resected who have progressed during or after treatment with a fluoropyrimidine and oxaliplatin based regimen with bevacizumab will be selected to participate in this study. The proposed eligibility criteria are anticipated to result in a study subject population representative of second-line mCRC patients who receive systemic therapy according to current practice guidelines.[14]

Subjects with second-line mCRC will be treated with FOLFIRI and ABT-165 instead of FOLFIRI in combination with bevacizumab, ziv-aflibercept, or ramucirumab (approved biological agents in second line CRC). The rationale for this approach is that the addition of bevacizumab, ziv-aflibercept, or ramucirumab provides a marginal improvement in mOS of 1.4 to 1.6 months beyond FOLFIRI alone and that ABT-165 through targeting both VEGF and DLL4 may provide an improved benefit compared to the approved biologic agents.

However, although ABT-165 can bind to both VEGF and DLL4 as demonstrated in preclinical and clinical studies, it is currently unknown if ABT-165 would provide less, similar or more benefit than the approved biological agents. Subjects will be fully informed in the Informed Consent Form, and during the consenting process, of the benefit and safety risks of receiving ABT-165 in place of one of the approved biological agents.

Selection of Doses in the Study

The dose of ABT-165 (2.5 mg/kg) selected for this study is based on analysis of PK, pharmacodynamic, safety, and efficacy data from a Phase 1 dose escalation study (Study M14-006) in subjects with advanced solid tumors. The dose selection is based on the monotherapy dose escalation/expansion (doses ranging from 1.25 – 7.5 mg/kg) and the combination of ABT-165 with FOLFIRI (ABT-165 doses ranging from 1.25 – 2.5 mg/kg). Monotherapy anti-tumor efficacy was observed at the lowest dose of ABT-165 (1.25 mg/kg) in an ovarian cancer subject. Monotherapy doses of ABT-165 of 3.75 mg/kg and above, although tolerable through the 28-day dose-limiting toxicity window, appeared to have toxicity i.e., gastrointestinal perforation and uncontrolled hypertension after further dosing. ABT-165 at 2.5 mg/kg plus FOLFIRI was tolerable through multiple cycles with some subjects experiencing stable disease or PR. A dose of ABT-165 of 2.5 mg/kg given intravenously with FOLFIRI every 2 weeks is expected to be efficacious with an acceptable safety profile. The starting dose of ABT-165 should be 1.25 mg/kg for first 2 cycles if the last dose of bevacizumab is within 6 weeks of ABT-165 treatment initiation. The dose of ABT-165 should then be increased to 2.5 mg/kg after 2 cycles of the 1.25 mg/kg dose.

Standard of care FOLFIRI and bevacizumab will be used in this study.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to randomization:
  - Bone marrow:
    - Absolute Neutrophil count (ANC) ≥ 1,250/µL;
    - Platelets ≥ 75,000/mm^3; (independent of platelet transfusions within 3 days prior to randomization);
    - Hemoglobin ≥ 8.0 g/dL (independent of red blood cell transfusions within 3 days prior to randomization).
  - Renal function:
    - Serum creatinine ≤ 1.5 × the institution's upper limit of normal (ULN) range or creatinine clearance ≥ 50 mL/min measured by 24-hour urine collection, or estimated using a Cockcroft-Gault calculation;
    - Proteinuria (Grade ≤ 1): urine dipstick ≤ 1+ (or urinalysis equivalent). If urine dipstick for proteinuria is ≥ 2+ (or urinalysis equivalent), subject is still eligible if a 24-hour urine collection has ≤ 1 gm protein.
  - Hepatic function and enzymes:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the ULN of institution's normal range. Subjects with liver metastases may have an AST and ALT of ≤ 5.0 × ULN;
    - Bilirubin: ≤ 1.5 × the ULN of institution's normal range.
  - Coagulation function
    - International normalized ratio (INR) ≤ 1.5 × and a partial thromboplastin time (PTT or aPTT) ≤ 1.5 × ULN if not receiving anticoagulation therapy
- 4. Are willing and able to comply with procedures required in this protocol.

Disease Activity

- 5. Diagnosis of histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum.
  - Primary tumor has been resected > 3 months prior to randomization.

- 6. Subject meets the following disease activity criteria:
  - At least 1 lesion on a computed tomography (CT) scan (preferred) or magnetic resonance imaging (MRI) that is measurable as defined by RECIST, Version 1.1.
  - Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.
  - Progression following treatment with 1 prior line of therapy in the metastatic setting
    - Prior therapy in first-line setting should have included a fluoropyrimidine (fluorouracil, capecitabine or tegafur), oxaliplatin, and bevacizumab, but not irinotecan or any other systemic chemotherapy for first-line treatment of metastatic disease
      - Maintenance therapy after discontinuation of oxaliplatin is considered part of first-line therapy
      - Subjects who received a local health authority-approved biosimilar bevacizumab antibody in 1L in place of bevacizumab will be eligible
  - PFS in first-line of therapy ≥ 3 months
- 7. Stratification factors (primary tumor location and RAS status) are known at time of randomization.
  - Subject is B-RAF wild type if tested (if B-RAF status is unknown, test is not required)
- 8. Subject does not have known uncontrolled metastases to the central nervous system (CNS). Subjects with treated brain metastases that are radiographically stable (for at least 2 weeks after therapy) and have no evidence of cavitation or hemorrhage in the brain lesion(s), are eligible provided that they are asymptomatic and do not require systemic corticosteroids (subjects must have discontinued systemic steroids specifically for brain metastases at least 1 week prior to randomization).
  - No history of carcinomatous meningitis or untreated active spinal cord compression.
  - No history of neurosurgical resection of CNS metastasis within 90 days prior to randomization.

Subject History

- 9. No history of Gilbert's syndrome or the following UGT1A1 genotypes if tested: UGTA1*6/*6, UGT1A1*28/*28 or UGT1A1*6/*28 or any other genotype known to increase irinotecan toxicity.
- 10. No unresolved clinically significant toxicities from prior anticancer therapy, defined as any Common Terminology Criteria for Adverse Events (CTCAE) that has not resolved to Grade ≤ 1 with the exception of peripheral neuropathy which must have resolved to Grade ≤ 2 and except where otherwise noted in the eligibility criteria.
- 11. No active clinically significant condition(s) that might put the subject at higher risk for anti-angiogenic therapy:
  - Symptomatic or persistent, uncontrolled hypertension defined as either systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 90 mmHg
    - Subjects may be on up to 2 antihypertensive medications to achieve this level of control.

  - Combination antihypertensive agents consisting of 2 different medications will be considered as 2 antihypertensive medications.
  - Subjects must be on stable doses of antihypertensive medications with stable blood pressure in the 7 days prior to randomization.
- Prior history of clinically significant: pulmonary hypertension, uncontrolled systemic hypertension or hypertensive crisis, symptomatic heart failure (Heart Association class III – IV), cardiomyopathy, myocardial infarction, unstable/severe angina pectoris, active cardiac arrhythmia, coronary/peripheral artery bypass graft, aneurysm or aneurysm repair, angioplasty, cerebrovascular accident or transient ischemic attack within 1 year of randomization.
- Left ventricular ejection fraction (LVEF) < 50%.
- Evidence for pulmonary hypertension as defined by peak tricuspid velocity (TV) > 2.5 m/s on Doppler ECHO.
  - Subjects who have inadequate (unmeasurable) tricuspid regurgitation Doppler signal are eligible provided they do not have other evidence for pulmonary hypertension.
- Brain natriuretic peptide (BNP) 2 × above the normal institutional range (i.e., > 200 pg/mL).
- History of any of the following during first-line therapy with a bevacizumab-containing regimen: arterial thrombotic/thromboembolic event, bowel perforation, Grade 4 hypertension, Grade 3 proteinuria, or Grade 3 – 4 bleeding event.
- Non-healed wound, ulcer, or bone fracture.
- Osteonecrosis of the jaw.
- Subject has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization or is anticipated to have a major surgical procedure during the course of the study.
- Subject had minor surgical procedures, such as fine needle aspirations or core biopsies, within 7 days prior to randomization.
- Subject has radiologic evidence of tumor invading or encasing a major blood vessel.
- Subject with history of esophageal varices or bleeding peptic ulcer or erosive esophagitis or gastritis < 3 months prior to randomization.
- Subject has history of significant bleeding (Grade ≥ 2) < 3 months prior to randomization.
- Subject has history of deep venous thrombosis or pulmonary embolism < 3 months prior to randomization.
  - Subject may be on maintenance anticoagulation at time of randomization as long as they have not had clinically significant bleeding within 14 days prior to randomization.
- Subject has used nonsteroidal anti-inflammatory agent (within 7 days prior to randomization) or aspirin > 325 mg/day or other agents known to irreversibly inhibit platelet function (within 14 days prior to randomization) or subject has a condition that requires use of high dose steroids or chronic nonsteroidal anti-inflammatory agent administration.

- Subject has high risk of gastrointestinal perforation or fistula formation in the judgment of the Investigator or Medical Monitor.
  - Subject with active ulcerative colitis, Crohn's disease, or inflammatory bowel disease < 1 year prior to randomization.
  - Subject with history of fistula or abdominal irradiation.
  - Subject with clinical (including paralyzed bowel, ileus, or mechanical obstruction) or radiographic evidence of partial or complete gastrointestinal obstruction < 3 months prior to randomization.
  - Subject with history of gastrointestinal perforation or fistula including tracheo-esophageal fistula.
  - Subject with clinical history of diverticulitis with evidence of diverticuli by CT scan or colonoscopy.
  - Subject with extensive peritoneal carcinomatosis or bulky abdominal disease.
  - Subject has history of ascites requiring paracentesis < 6 months prior to randomization.

- 12. No history of **prior malignancy** except for successfully treated Non-Melanoma Skin Cancer, localized carcinoma in situ of the cervix, adequately treated Stage I or II cancer from which the subject is currently in complete remission, or any other cancer from which the subject has been disease free for at least 2 years.
- 13. No history of clinically significant (per Investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 14. No history of clinically significant medical conditions or any other reason that in the opinion of the Investigator would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 15. No history of an **allergic reaction** or significant sensitivity to constituents of the study drugs (and its excipients) and/or other products in the same class.
- 16. No clinically relevant or **significant ECG abnormalities**.
- 17. No history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.
- 18. No history of prior autologous or allogeneic organ or transplantation.
- 19. No history of active infection requiring parenteral antibiotic, antifungal, or antiviral therapy.
- 20. No ongoing treatment for active Hepatitis B virus (prophylaxis allowed) or Hepatitis C virus
  - Subject with documented cure after anti-viral therapy may be enrolled.
- 21. No known human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness.
- 22. No history of cirrhosis at a level of Child-Pugh B (or worse); or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from the cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis

Contraception

- 23. A **negative serum pregnancy test** for all female subjects (except post-menopausal) at the Screening Visit and a negative urine pregnancy test for all female subjects (except post-menopausal) at baseline prior to the first dose of study drug.
- 24. **If female**, subject must be either **postmenopausal**, OR permanently **surgically sterile** OR for women of childbearing potential (WOCBP) practicing at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 6 months after the last dose of study drug.
- 25. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 6 months after the last dose of study drug, to practice the protocol-specified contraception.
- 26. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for approximately 6 months after the last dose of study drug.
- 27. Male who is not considering **fathering a child or donating sperm** during the study or for approximately 6 months after the last dose of study drug.

Concomitant Medications

- 28. Subject must have **discontinued prior anticancer therapy at least 21 days** prior to randomization, with resolution of any toxicity from prior therapy.
  - Palliative radiation therapy for bone or skin metastases or subcutaneous metastatic nodules for 10 fractions or less is not subject to a washout period.
- 29. Subject must not currently be enrolled in another therapeutic clinical study.
- 30. Subject must not have been treated with **any agent known to target DLL4**.
- 31. Subject must not have received **any live vaccine** within 4 weeks prior to randomization, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.
  - Subject may not get inactivated vaccines within a 3-day window of receiving study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level > 40 IU/L.

If female, subject must be either post-menopausal, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) or a WOCBP and must practice at least 1 of the

following methods of birth control, throughout the study including 6 months after the last study drug dose is given.

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
- Bilateral tubal occlusion/ligation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner(s) provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception Requirements for Males

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 6 months after the last dose of study drug to use condoms and his female partner(s) must use at least 1 of the contraceptive measures (as defined above for female study subjects of childbearing potential).

5.3 Prohibited Medications and Therapy

During the study any anti-cancer agents, anti-cancer medicinal/herbal remedies, anti-cancer hormonal therapy, and other investigational drugs are prohibited. Cannabinoids are not prohibited for treating pain, nausea, anorexia, etc.

Palliative radiation therapy for bone or skin metastases or subcutaneous metastatic nodules for 10 fractions or less is allowed if the subject is otherwise stable.

Subjects should not receive live vaccines during the study.

5.4 Prior and Concomitant Therapy

Non-steroidal anti-inflammatory drugs such as ibuprofen are allowed but preferably after end of Cycle 1 and at lowest doses that are needed to achieve desired results. Use of salicylates such as acetylsalicylic acid (Aspirin) > 325 mg/day is discouraged and should be avoided.

All subjects should be highly encouraged to have excellent bowel care consisting of high fiber diet or supplemental fiber and/or stool softeners with adequate oral hydration to reduce diverticulitis or constipation.

Any medication or vaccine (including over the counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie Medical Monitor (SPONSOR/Emergency Medical Contact).

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 2 weeks prior to randomization, whichever is longer. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject will be withdrawn from ABT-165/bevacizumab and FOLFIRI treatment at any time for reasons including, but not limited to, the following:

- The subject experiences radiographic disease progression (as defined by RECIST version 1.1).
- The subject's response to therapy is unsatisfactory, as evidenced by clinically significant and clearly documented progression of disease.
- The subject requires alternate anti-cancer agents during the study period.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of study drug(s), as determined by the Investigator or the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drugs would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drugs would place the subject at risk.
- The subject becomes pregnant while on study drugs.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial.

ABT-165/bevacizumab will be permanently discontinued if any of the following AEs occur but subject may remain on FOLFIRI and on study until radiographic progression after resolution of toxicity as deemed appropriate by the Investigator:

- Gastrointestinal perforation or fistula formation involving an internal organ.
- Serious (Grade ≥ 3) hemorrhage.

- Arterial thromboembolic events (e.g., myocardial or cerebral infarction) of any grade.
- Documented blood pressure in triplicate of systolic ≥ 180 or diastolic ≥ 110 mmHg (either systolic or diastolic exceeded on all 3 readings).
- Hypertensive crisis or hypertensive encephalopathy.
- Reversible posterior leukoencephalopathy syndrome (RPLS).
- Nephrotic syndrome (Grade 3 proteinuria).
- Grade 4 infusion-related reaction (IRR).
- Necrotizing fasciitis.
- Class III or IV heart failure (including Grade ≥ 2 congestive heart failure).
- Acute coronary syndrome (including cardiac ischemia).
- Drop in LVEF to < 40% or an LVEF of 40% – 45% with a 10% or greater absolute decrease below pretreatment values.
- Pulmonary hypertension Grade 3 or 4

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the Investigator. The Investigator may also stop the study at his/her site if he/she has safety concerns.

In the event AbbVie is notified in writing that a subject withdraws consent to participate in the clinical study, and no longer consent to the biomarker research and/or the optional biomarker research, no new biomarker data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from mandatory and/or optional biomarker research collected before subject withdrawal of consent will remain part of the study results.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study treatment but have not progressed radiographically, should continue to be followed by imaging until progression, unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue study treatment early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30/90-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved, unless another anti-cancer therapy is started in the interim.

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic case report form (eCRF) page.

5.7 Study Drugs

ABT-165 (2.5 mg/kg or 1.25 mg/kg for the first 2 cycles, see below) plus FOLFIRI (irinotecan – 180 mg/m^2; leucovorin (folinic acid) – DL-400 mg/m^2 or L-200 mg/m^2; fluorouracil – bolus: 400 mg/m^2, then continuous infusion: 1200 mg/m^2/day × 2 days - total of 2400 mg/m^2 over 46 – 48 hours) or bevacizumab (5 mg/kg) plus FOLFIRI will be administered via intravenous (IV) infusion on Day 1 of each 14-day cycle. The Investigator may adjust the suggested FOLFIRI dosing based on Institutional guidelines and best medical practice. The first infusion of ABT-165 or bevacizumab will be administered over 60 (± 10) minutes. If the first infusion is tolerated, the second and subsequent infusions will be administered over 30 (± 10) minutes as tolerated. For those subjects who required a 90 minute (or longer) infusion of bevacizumab in the first-line setting, the first infusion of ABT-165 or bevacizumab will be administered over 90 (± 10) minutes and may be decreased to 60 (± 10) minutes and 30 (± 10) minutes as tolerated.

The dose of ABT-165/bevacizumab does not need to be adjusted unless the subject's measured weight changes by > 10% from baseline or the subject has received bevacizumab within 6 weeks of the first dose of ABT-165. The starting dose of ABT-165 should be 1.25 mg/kg for first 2 cycles if the last dose of bevacizumab was within 6 weeks of ABT-165 treatment initiation. The dose of ABT-165 should then be increased to 2.5 mg/kg after 2 cycles of the 1.25 mg/kg dose.

Dosing of bevacizumab may follow site's standard of care guidelines.

ABT-165 will be provided as lyophilized powder and bevacizumab may be provided as solution for IV injection. ABT-165, bevacizumab, and FOLFIRI treatment will be open to investigators and subjects.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Study drug will only be used for the conduct of this study.

Instructions for drug preparation will be provided by AbbVie.

AbbVie will not routinely supply drugs other than ABT-165. AbbVie may provide Bevacizumab and FOLFIRI at some sites depending on operational or regulatory requirements. Non-investigational medicinal product (standard of care) must be obtained commercially.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects will be randomized in a 1:1 ratio to ABT-165 plus FOLFIRI or to bevacizumab plus FOLFIRI. Randomization will be stratified by subjects' RAS status (mutation in K-RAS or N-RAS yes vs no) and tumor location (right-sided vs left-sided). Permuted block randomization method will be used to allocate treatments. The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying IEC/ IRB, regulatory authorities (as applicable) and AbbVie.

5.10 Tumor Assessments (Radiologic)

A CT scan of all areas of metastatic disease (including the chest, abdomen, and pelvis) using RECIST, Version 1.1 will be used in the evaluation of tumor responses. If the subject is unable to undergo a CT scan with IV contrast due to allergy or renal insufficiency, a non-contrast CT may be performed. Magnetic resonance imaging (MRI) can be conducted instead of CT scans in cases where local laws/requirements mandate or when an MRI would be a better tool for tumor assessments. Subjects are to continue monitoring by the same methods unless evidence of tumor metastasis warrants otherwise or a medical contraindication is noted.

Baseline tumor assessments must be conducted at Screening within 28 days before randomization. Post-baseline tumor assessment will be conducted approximately every 8 weeks from Cycle 1 Day 1 (C1D1) until radiographic progression. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Scheduled tumor assessments should be performed prior to the administration of study drug. Tumor assessments should be performed every 8 weeks until a subject has evidence for radiographic progression. An unscheduled tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression (including clinical progression), and no scan has been performed within the last 28 days.

Response criteria will be assessed using RECIST, Version 1.1. Disease progression will be defined as radiographic progression of disease by RECIST, Version 1.1. (Appendix B of the Operations Manual (Appendix F)), or clinical progression as determined by the Investigator (in which case every reasonable effort must be made to document radiographic progression).

For the purposes of this protocol, complete or PR do not need to be confirmed on a subsequent scan following initial documentation of the response.

AbbVie will require that sites electronically transfer copies of all CT or MRI scans used for radiographic tumor assessments. Instructions regarding procedures for transferring scans will be provided in a separate manual.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

The following standard SAE supplemental case report forms will be available and are to be used as applicable: Investigator SAE Supplemental, SAE Study Drug Information, SAE Supplemental Laboratory, SAE Supplemental Microbiology, and SAE Supplemental Procedure.

If an AE meets any of the following criteria, it is to be reported to AbbVie as a SAE within 24 hours of the site being made aware of the SAE:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 90 days after discontinuation of study treatment will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious adverse events and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- Uncontrolled hypertension: Grade 4
- Gastrointestinal perforation: any Grade
- Pulmonary hypertension: ≥ Grade 2
- Proteinuria: Grade 3 (nephrotic syndrome)

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate or severe according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity. The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject or in the partner of a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancies in study subject's partners will be collected from the date of the first dose through 6 months following the last dose of study drug.

The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described below. This includes, but is not limited to, AEs of uncontrolled hypertension, gastrointestinal perforation, and pulmonary hypertension. This also includes the following laboratory abnormality: proteinuria.

For observed toxicities, subjects should be assessed for inter-current illness or other causes and treated as appropriate. While Investigator discretion and best medical practice should be used for subject management with regards to toxicities, some suggested guidelines are given below and in the sections referenced.

General Considerations for Toxicity Management

If a subject experiences AEs during a cycle, the subject will complete the planned activities of the cycle as scheduled per the Treatment Period Visit Activities Tables (Section 2.1 of the Operations Manual) (i.e., vital signs, labs, radiographic tumor assessment, etc.) before resuming protocol therapy.

If a dose interruption is needed, the subject will continue to have study visits as planned; however, pharmacodynamics and/or PK samples will not be collected during this period. Dose interruptions for events that are clearly not related to the protocol therapy (e.g., underlying cancer, planned surgical procedures, or acute viral illnesses) should not necessitate a dose reduction for FOLFIRI. The timing of dose resumption should be at the discretion of the Investigator; pharmacodynamics and/or PK sample collection should restart as indicated once subjects have resumed dosing.

Best supportive care and treatment will be given as appropriate to each subject e.g., antiemetics, antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain or cough, drugs for prevention of skeletal-related events or osteoporosis. A new cycle of chemotherapy treatment in general may not begin until the ANC is ≥ 1,250/mm^3, the platelet count is ≥ 75,000/mm^3, and any treatment-related gastrointestinal toxicity has resolved to ≤ Grade 1. For subjects whose blood counts do not meet the above standards, the Investigator may use their judgment and clinical best practice

standards to determine if it is in the best interest of the subject to continue dosing FOLFIRI, potentially at a reduced dose, or hold FOLFIRI until recovery of blood counts. If the initiation of a new cycle is delayed for > 4 weeks, Investigators should contact the Study Designated Physician regarding ongoing clinical benefit prior to resumption of protocol therapy.

ABT-165/bevacizumab can be given with FOLFIRI or irinotecan or 5-FU/LV. ABT-165/bevacizumab can be continued even after discontinuation of FOLFIRI. FOLFIRI or irinotecan or 5-FU/LV can be continued even if ABT-165/bevacizumab is discontinued. No dose reductions of ABT-165/bevacizumab are allowed. General guidance for dose reduction of FOLFIRI is given below; however, Investigators should use their judgment and are allowed to follow best medical practice and Institutional standards.

Dose Reductions and Delays for FOLFIRI Toxicity

Dose modification for the current cycle and reduction for subsequent cycles may be carried out as shown below (Table 1). Dose adjustments of irinotecan and 5-FU infusion may be made independently based on the specific types of toxicities observed as discussed below. For the purposes of this study, only 3 dose reductions of FOLFIRI are allowed. If a dose reduction is required beyond dose level –3 for irinotecan, discontinue irinotecan use, but continue ABT-165/bevacizumab, 5-FU and leucovorin. If a dose reduction is required beyond dose level –3 for 5-FU, discontinue 5-FU but ABT-165/bevacizumab may continue until disease progression or intolerable toxicity.

Note: The 5-FU bolus can only be skipped or discontinued.

Table 1. FOLFIRI Dose Reductions

Drug*	Starting Dose	Dose Level –1	Dose Level –2	Dose Level –3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	100 mg/m^2
5-FU Infusion	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2	1360 mg/m^2
5-FU Bolus	400 mg/m^2	Discontinued	Discontinued	Discontinued

* Leucovorin (LV) may be administered as DL- 400 mg/m^2 or L-200 mg/m^2 IV prior to the 5-FU infusion. However, LV may also be administered or omitted per Institutional standards. If an infusion of 5-FU needs to be skipped, leucovorin must also be skipped.

Toxicity Management Guidelines for Protocol Therapy

In addition to AEs of special interest, uncontrolled hypertension, gastrointestinal perforation, pulmonary hypertension, and proteinuria, the following AEs are addressed in this section: hematologic toxicities, gastrointestinal toxicities, pulmonary toxicities, cardiovascular toxicities, posterior reversible leukoencephalopathy syndrome (RPLS/PRES), wound dehiscence, gastrointestinal perforation, intra-abdominal fistula, hypersensitivity, and infusion reactions.

Hematologic Toxicities:

No ABT-165/bevacizumab dose modifications will be made for hematologic toxicity. Subjects may receive ABT-165/bevacizumab while 5-FU infusion and irinotecan are suspended for resolution of hematologic toxicity unless they have febrile neutropenia (see below).

The following dose modifications are recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 of any cycle):

- Grade 2 neutropenia or thrombocytopenia, discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan 1 dose level for the next cycle. For each subsequent cycle, may resume 5-FU infusion and irinotecan at the previous dose levels, provided ANC ≥ 1,250/µL and platelets ≥ 75,000/mm^3.
- Grade 3 or 4 neutropenia or thrombocytopenia, suspend chemotherapy (FOLFIRI). If counts recover to ANC ≥ 1,250/µL and platelets ≥ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at 1 lower dose level.
- Febrile neutropenia (defined as ANC < 1000/µL and T ≥ 38.5°C), suspend all protocol therapy. If fever resolves, and counts recover to ANC ≥ 1,250/µL and platelets ≥ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at 1 lower dose level.

Gastrointestinal Toxicities:

Gastrointestinal Perforation or Intra-Abdominal Fistula: For any grade gastrointestinal perforation, or intra-abdominal fistula: Discontinue ABT-165/bevacizumab.

Diarrhea: Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. It is strongly suggested that Atropine, 0.25 – 1.0 mg IV or 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. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

Late diarrhea (e.g., developing more than 24 hours after irinotecan) should be managed with loperamide as described below.

The following concomitant medications and/or dose modifications are 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:

- 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).

- For Grade 2 diarrhea, discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan 1 dose level for the next cycle. For each subsequent cycle, resume 5-FU infusion and irinotecan at the previous dose levels, provided diarrhea has fully resolved.
- For 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 1 lower dose level.

For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, subjects will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of 1) a poorly formed or loose stool or 2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or 3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Subjects may take loperamide 4 mg every 4 hours during the night. The maximum daily dose of loperamide is 16 mg/day. Subjects should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the Investigator. Subjects should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

Mucositis: The following dose modifications are based on the grade of mucositis seen on the day of treatment for any day after Day 1 in any cycle.

- For Grade 2 mucositis, may discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan 1 dose level for the next cycle. For each subsequent cycle, may resume 5-FU infusion and irinotecan at the previous dose levels, provided mucositis has fully resolved.
- For 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 1 lower dose level.

Nausea/Vomiting: The following dose modifications are based on the grade of nausea and vomiting occurring during a cycle (i.e., after Day 1 in any cycle).

- For Grade 3 nausea or vomiting, reduce irinotecan 1 dose level for the next cycle. For each subsequent cycle, may continue irinotecan at previous dose level, provided nausea has resolved ≤ Grade 2.
- For Grade 4 nausea or vomiting, discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at 1 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. The use of aprepitant is prohibited for those patients receiving FOLFIRI.

Pulmonary Toxicities

- For ≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates, hold ABT-165/bevacizumab and irinotecan until interstitial lung disease is ruled out. 5-FU/leucovorin

may be continued based on Investigator judgment. Discontinue all protocol therapy if interstitial lung disease is confirmed.

Dose Delays and Discontinuation for ABT-165/Bevacizumab Toxicity

ABT-165 is always administered at 2.5 mg/kg IV. ABT-165 may be delayed or discontinued, but the dose will not be reduced.

Bevacizumab is always administered at 5 mg/kg IV. Bevacizumab may be delayed or discontinued, but the dose will not be reduced.

For certain toxicities described in the Protocol, ABT-165/bevacizumab will be permanently discontinued but subject may remain on FOLFIRI after resolution of toxicity if deemed appropriate by the Investigator.

Pulmonary Hypertension

Subjects with TV of ≥ 3.7 m/s on ECHO must have ABT-165/bevacizumab held. FOLFIRI dosing may continue as tolerated. A repeat ECHO should be performed every month. When the TV is ≤ 3.0, dosing with ABT-165/bevacizumab may resume with monthly ECHO. If repeat ECHO shows TV ≥ 3.7, ABT-165/bevacizumab must be permanently discontinued.

Cardiovascular Toxicities:

Hypertension

The following general guidance is given for Investigators to maintain the majority of blood pressures < 150/90 mmHg with the use of antihypertensive medications, dose delays and discontinuation of ABT-165/bevacizumab. In general, antihypertensive therapy should be started or intensified as soon as blood pressure is ≥ 150/90 mmHg or systolic blood pressure has increased by 20 mmHg and should be titrated promptly to maximum approved doses. The Principal Investigator may consult with or refer the subject to physicians trained in the management of hypertension. Subjects who have difficulty to control hypertension (for example multiple blood pressure readings ≥ 160/100 mmHg) should be discussed with the Medical Monitor. Subjects may receive up to 4 different antihypertensive medications at any 1 time to control hypertension.

Subjects requiring more than 4 different antihypertensive medications to maintain the majority of their blood pressures < 150/90 mmHg will have their dose of ABT-165/bevacizumab held and may be resumed once blood pressures is < 150/90 mmHg on the day of dosing and they are on 4 or fewer antihypertensive agents.

The preferred usage of antihypertensive medication is as follows:

- Calcium channel blocker (dihydropyridines)
- Angiotensin receptor blocker or Angiotensin-converting enzyme (ACE) inhibitor (but not used simultaneously)
- Beta adrenergic blocker (not to be used in subjects with heart rate ≤ 50)
- Centrally acting sympathetic agonist (i.e., clonidine)

- Diuretic

The Investigator should use best medical practice in treating hypertension given the general guidance above.

Thrombotic Events

Subjects should be carefully monitored for evidence of thromboembolic disease during treatment.

Venous Thrombotic Events

- For Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Skip ABT-165/bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, ABT-165/bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, ABT-165/bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:
  - The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on stable dose of low molecular weight heparin prior to restarting ABT-165/bevacizumab treatment;
  - The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels);
  - The patient must not have had hemorrhagic events (Grade ≥3) while on study.
- For Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of ABT-165/bevacizumab: Discontinue all protocol therapy.
- For symptomatic pulmonary embolism, subjects will discontinue all protocol therapy.

Arterial Thrombotic Events

- For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue ABT-165/bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue ABT-165/bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cardiac ischemia/infarction, discontinue all protocol therapy.
- For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol therapy.

Left Ventricular Dysfunction

- For Grade 3 left ventricular dysfunction, discontinue ABT-165/bevacizumab. Subjects may continue other protocol therapy.
- For Grade 4 left ventricular dysfunction, discontinue all protocol therapy.

Hemorrhage/Bleeding

- For Grade 3 hemorrhage/bleeding, discontinue ABT-165/bevacizumab and skip other protocol therapy; once hemorrhage or bleeding resolves, other protocol therapy may be continued at the treating physician's discretion.
- For Grade 4 hemorrhage/bleeding, discontinue all protocol therapy.

Posterior Reversible Leukoencephalopathy Syndrome (RPLS/PRES)

For signs and symptoms suggestive of RPLS (e.g., confusion, headache, seizures, cortical blindness) skip ABT-165/bevacizumab. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, ABT-165/bevacizumab should be permanently discontinued.

If RPLS is ruled out via MRI, the decision on resuming ABT-165/bevacizumab should be based on the nature of the signs/symptoms. For Grade 4 events with likely relationship to ABT-165/bevacizumab, discontinue ABT-165/bevacizumab; for Grade 3 events, ABT-165/bevacizumab may be resumed if toxicities completely resolve within 4 weeks.

Other protocol therapy may be continued at the discretion of the Investigator.

Proteinuria

Moderate to severe proteinuria pending further evaluation

- Subjects with a 2+ urine protein dipstick (or urinalysis equivalent) reading may receive their scheduled dose of ABT-165/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 ABT-165/bevacizumab.
- Subjects with a 3+ or greater urine protein dipstick (or urinalysis equivalent) reading may have their protein dipstick (or urinalysis) repeated and if still 3+ or greater should not receive their scheduled dose of ABT-165/bevacizumab until the results of a 24-hour urine protein analysis are available.
- Suspend ABT-165/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 ABT-165/bevacizumab if subject develops nephrotic syndrome (Grade 3 proteinuria).

Sites that monitor urine protein measured by laboratory urinalysis (i.e., 30 mg/dL) may convert numerical terms to + terms and follow the protocol as generally outlined above or their Institutional standard of care.

Wound Dehiscence

- For wound dehiscence requiring medical or surgical intervention: Discontinue ABT-165/bevacizumab.

Hypersensitivity and Infusion Reactions

Note that the NCI CTCAE defines these reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., mAbs or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the CTCAE version 4.0 for a complete list of signs and symptoms of "Cytokine release syndrome/acute infusion reaction;" and see the "Allergy/Immunology" section for a description of hypersensitivity.

ABT-165/Bevacizumab Dose Modifications for Infusion Reactions

The initial ABT-165/bevacizumab dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur, the second and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated. Patients may receive premedication with diphenhydramine 25 to 50 mg intravenously or orally 30 minutes prior to ABT-165/bevacizumab if they have previously experienced mild infusion reactions. Acetaminophen premedication may also be used.

Infusion Modifications for Hypersensitivity Reactions

- For Grade 1 hypersensitivity reactions (transient rash, drug fever < 38°C): Decrease the infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
- For Grade 2 hypersensitivity reactions (urticaria, drug fever ≥ 38°C and/or asymptomatic bronchospasm): Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to institutional policy.
- For Grade 3 or Grade 4 hypersensitivity reactions: Stop the infusion. Discontinue all protocol treatment and notify the Study Designated Physician.

Other Non-Hematologic Toxicities

- For all other ≥ Grade 3 clinically significant non-hematologic toxicities not described above, hold all protocol therapy and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 or baseline within 4 weeks, protocol therapy may be resumed. Dose modification of FOLFIRI and dosing delays of ABT-165/bevacizumab will be at the discretion of the Investigator.

For allowed study drug interruption, the following rules apply:

1. Some types of elective surgery will be allowed during this study (i.e., cataract surgery) but only after consultation with the Medical Monitor. For elective surgery, the following guidelines have to be followed: Discontinue treatment with ABT-165/bevacizumab at least 28 days prior to elective surgery. Do not initiate ABT-165/bevacizumab for at least 28 days after surgery and until the surgical wound is fully healed.

2. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, reintroduction of study drug is allowed 28 days after surgery provided that it is safe to do so and once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.3 Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The primary efficacy analysis will be conducted when approximately 60 PFS events are accrued. Based on the assumption of median PFS of 5.7 months in control arm, [redacted]

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The intent to treat (ITT) population includes all randomized subjects. The ITT will be used for all efficacy and baseline analyses. Subjects will be grouped according to treatment as randomized. The Per-Protocol Analysis Set represents a subset of the ITT who received at least 1 dose of study drug and without any major violations. Definitions of major protocol violations will be detailed in the SAP. Additional analysis may be conducted on the Per-Protocol Analysis Set, in order to evaluate the impact of major protocol violations.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

Primary Analysis

Analysis of the primary endpoint (PFS) will be conducted on the ITT population.

The HR of PFS of ABT-165 plus FOLFIRI compared to bevacizumab plus FOLFIRI will be estimated using the stratified Cox model. Progression free survival will be defined as the time from randomization until the first occurrence of radiographic progression, as determined by a blinded independent central review, or death from any cause. Progression free survival time for subjects without PFS events will be censored at the time of last tumor assessment. The stratification factors for the stratified Cox model will be the stratification variables used in the randomization. This primary analysis will include a 90% confidence interval (CI) for the estimated stratified HR for PFS. Kaplan-Meier methodology will also be used to estimate the PFS curve, median PFS and its associated 90% CI in each treatment arm. Results from a stratified and unstratified log-rank test will also be presented.

Sensitivity analysis of the primary endpoint (PFS) will be conducted on the Per-Protocol Analysis population.

Secondary Analysis

Overall Survival (OS): Duration of OS is defined as the time from randomization until death from any cause. Duration of survival for subjects who are still alive at the time of analysis will be censored on the date of last contact. The same method used in the PFS analysis will be used for the OS analysis.

Objective Response Rate (ORR): ORR will be defined as the proportion of subjects with a CR or PR as determined by blinded independent central review based on RECIST, Version 1.1. The ORR will be estimated in each treatment arm. The 90% CI of the estimated ORR will be provided.

Details on the primary and other efficacy analyses are provided in the SAP.

Sample Size Estimation

The planned total sample size of approximately 100 subjects for this study is based upon the precision of estimating the HR for PFS with a total of 60 PFS events. The median PFS of subjects in second-line mCRC treated with bevacizumab plus FOLFIRI is 5.7 months. Based on a minimum of 60 PFS events, if a HR of 0.74 (or an increase in median PFS from 5.7 to 7.7 months assuming exponential PFS) is observed, the approximate 90% CI for the HR would be (0.48, 1.13). An observed HR of 0.66 (median PFS increases from 5.7 to 8.6 months) would have the approximate 90% CI of (0.43, 1.01). This study is intended to be hypothesis-generating.

7.4 Statistical Analyses for Safety

Safety will be assessed by evaluating study drug exposure, AEs, SAEs, all deaths, as well as changes in laboratory data and vital signs. Subjects who are randomized but do not receive study drug (ABT-165) or bevacizumab will not be included in the analyses of safety. Safety analysis results will be presented by treatment group. Subjects will be grouped according to the actual treatment received.

Details on the safety analyses are provided in the SAP.

7.5 Data Monitoring Committee (DMC)

An internal DMC comprised of persons independent of the AbbVie study team and with relevant expertise in their field will be established to review unblinded safety data initially approximately 6 months after the first subject is enrolled and approximately every 3 months thereafter. Furthermore, the DMC will also review the available efficacy data approximately every 3 months. The efficacy portion of the analysis for the DMC review will be based on investigator assessment. The purpose of the review of efficacy data in addition to safety is to ensure an adequate benefit to risk ratio is being maintained and to enable further development activities.

Gastrointestinal perforation is 1 of the AEs of special interest and as such, the DMC is required to monitor this event closely. If the observed rate of gastrointestinal perforation meets both of the following conditions at any time, the DMC may recommend stopping the study:

- 90% lower bound of the observed gastrointestinal perforation rate in the ABT-165 arm is > 5%.
- The observed gastrointestinal perforation rate in the ABT-165 arm is statistically significantly higher than the observed gastrointestinal perforation rate in the bevacizumab arm ($P < 0.10$).

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews and relevant safety data to be assessed.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual (Appendix F), International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the Investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of last subject's last survival follow-up contact. The sponsor may also end the study at any time.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AIA	Administrative Interim Analysis
ANC	Absolute Neutrophil Count
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BNP	Brain Natriuretic Peptide
C1D1	Cycle 1 Day 1
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLL4	Delta-Like Ligand 4
DMC	Data Monitoring Committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
5-FU	Fluorouracil
FOLFIRI	Irinotecan/Fluorouracil (5-FU)/Leucovorin (Folinic Acid) with bolus and continuous infusion 5-FU
FOLFOX	Leucovorin/Fluorouracil/Oxaliplatin
GCP	Good Clinical Practice
HR	Hazard Ratio
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board

IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
ITT	Intent To Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
mOS	Median Overall Survival
MRI	Magnetic Resonance Imaging
nAb	Neutralization effect of the ADA
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	Overall Survival
ORR	Objective Response Rate
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PTT	Partial Thromboblastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reactions
TV	Tricuspid Velocity
ULN	Upper Limit of Normal
WOCBP	Woman of Childbearing Potential
VEGF	Vascular Endothelial Growth Factor

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M14-064: ABT-165 plus FOLFIRI vs Bevacizumab plus FOLFIRI in mCRC Previously Treated with Fluoropyrimidine, Oxaliplatin and Bevacizumab

Protocol Date: 07 February 2019

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual (Appendix F), and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Clinical Program Development
		Bioanalysis
		Clinical Oncology
		Clinical Pharmacology/Clinical PK
		Data and Statistical Sciences
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities for this study. The individual activities are described in detail in the **Operations Manual**.

Study Activities Table

Activity	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle ≥ 4	Every 8 weeks from C1D1 (±1 week)	Final Visit (30 [±15] days after last dose)	Follow-Up (90 [±15] days after last dose, then every 90 [±15] days)
	Up to 28 days before Randomization	Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 1 (±2 days)	Day 1 (-2 days to +5 days)			
INTERVIEWS										
Subject Information and Informed Consent	✓									
Eligibility Criteria	✓									
Medical and Cancer History	✓	✓								
Performance Status (ECOG)	✓	✓		✓		✓	✓		✓	
Adverse Event Assessment	✓	✓	✓	✓	✓	✓	✓		✓	✓
Prior/Concomitant Therapy	✓	✓	✓	✓	✓	✓	✓		✓	
Post-treatment Cancer Information										✓
Date and Cause of Death										✓
Local LABS & EXAMS										
Complete Physical Exam	✓									
Symptom-directed Physical Exam		✓	✓	✓	✓	✓	✓		✓	
Vital Signs (BP measured in triplicate)	✓	✓	✓	✓	✓	✓	✓		✓	

Activity	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle ≥ 4	Every 8 weeks from C1D1 (±1 week)	Final Visit (30 [±15] days after last dose)	Follow-Up (90 [±15] days after last dose, then every 90 [±15] days)
	Up to 28 days before Randomization	Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 1 (±2 days)	Day 1 (-2 days to +5 days)			
Serum or Urine pregnancy test (Subjects of childbearing potential only)	✓	(✓)				✓	Odd cycles only		✓	Monthly for 6 months
Hematology	✓	(✓)	✓	✓	✓	✓	✓		✓	
Chemistry	✓	(✓)	✓	✓	✓	✓	✓		✓	
Urinalysis	✓	(✓)		✓		✓	✓		✓	
aPTT/PT/INR	✓									
BNP	✓									
12-lead ECG	✓							✓	✓	
Cardiac ECHO	✓							✓		
Tumor Assessment (CT Scan/MRI)	✓							✓	✓	
Central LABS										
Hematology	✓	(✓)	✓	✓	✓	✓	✓		✓	
Chemistry	✓	(✓)	✓	✓	✓	✓	✓		✓	
Urinalysis	✓	(✓)		✓		✓	✓		✓	
aPTT/PT/INR	✓									
BNP and CEA tests	✓					✓	Odd cycles only		✓	
PK Sample		✓				✓	Cycle 7, 11, 15 and 19		✓	

Activity	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle ≥ 4	Every 8 weeks from C1D1 (±1 week)	Final Visit (30 [±15] days after last dose)	Follow-Up (90 [±15] days after last dose, then every 90 [±15] days)
	Up to 28 days before Randomization	Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 1 (±2 days)	Day 1 (-2 days to +5 days)			
ADA/nAb Sample		✓				✓	Cycle 7, 11, 15 and 19		✓	
Biomarker plasma Sample		✓		✓		✓	Cycle 8 only		✓	
Biomarker Whole Blood Sample		✓		✓		✓				
Archival Tumor Samples or Fresh Biopsy Block/ Slides	✓									
Tumor Biopsy at Progression (Optional)									✓	
Pharmacogenetic Whole Blood (DNA) (Optional)		✓				✓				
IRT										
Register subject information and screening visit	✓									
Randomization/Drug Assignment (≤ 3 days prior to Cycle 1 Day 1)	✓									

Activity	Screening	Cycle 1		Cycle 2		Cycle 3	Cycle ≥ 4	Every 8 weeks from C1D1 (±1 week)	Final Visit (30 [±15] days after last dose)	Follow-Up (90 [±15] days after last dose, then every 90 [±15] days)
	Up to 28 days before Randomization	Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 1 (±2 days)	Day 1 (-2 days to +5 days)			
Rx TREATMENT										
Administer Study Drug (ABT-165 or bevacizumab)		✓		✓		✓	✓			
Administer FOLFIRI		✓		✓		✓	✓			

Abbreviations: ADA = antidrug antibody; aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; BP = blood pressure; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; nAb = Neutralization effect of the ADA; PK = pharmacokinetic; PT = prothrombin time

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	26 September 2017
Version 2.0	24 October 2018

The purpose of this Version is to modify ABT-165 dosing guidelines, edit eligibility criteria, and add stopping rules based upon occurrence of gastrointestinal perforation events, including the following:

- Updated Introduction

  Rationale: *To reflect the approval of a bevacizumab biosimilar (MVASI)*

- Added modified dosing guidelines to the protocol and operations manual for subjects who received bevacizumab within 6 weeks of ABT-165 treatment initiation

  Rationale: *To reduce risk of gastrointestinal perforation*

- Clarified that primary tumor must be resected > 3 months prior to randomization

  Rationale: *To reduce risk of gastrointestinal perforation*

- Modified eligibility criteria to exclude subjects who have conditions that require use of high dose steroids or chronic nonsteroidal anti-inflammatory agents

  Rationale: *To reduce risk of gastrointestinal perforation*

- Modified eligibility criteria to exclude subjects who have any history of fistula, abdominal irradiation, or diverticulitis

  Rationale: *To reduce risk of gastrointestinal perforation*

- Modified and clarified medications and therapy that are prohibited on study.

  Rationale: *For consistency with the Phase 1 study of ABT-165.*

- Added guidance for bowel care while on study

  Rationale: *To reduce risk of gastrointestinal perforation*

- Increased the frequency of DMC reviews of safety and efficacy data to every 3 months following the initial 6 month review

  Rationale: *To more closely monitor safety events during the study and to ensure an adequate benefit to risk ratio is being maintained*

- Introduced stopping rules for gastrointestinal perforation events

  Rationale: *To ensure subject safety*

In addition, minor clerical errors were corrected and edits for consistency within the document were made.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M14-064

Metastatic Colorectal Cancer: ABT-165 plus FOLFIRI vs Bevacizumab plus FOLFIRI in Metastatic Colorectal Cancer Previously Treated with Fluoropyrimidine, Oxaliplatin and Bevacizumab

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	ABT-165

1 CONTACTS

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2 INVESTIGATION PLAN

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about activity is provided in Operations Manual Section 3.

SCREENING:

(up to 28 days before randomization)

INTERVIEW	• Subject Information and Informed Consent • Eligibility Criteria • Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG) • Medical and Cancer History (including RAS status and primary tumor location needed for randomization)
EXAM	• Physical Exam (complete)[a] • Vital Signs (BP measured in triplicate) • 12-lead ECG	• Cardiac ECHO • Tumor Assessment (CT Scan/MRI)
LOCAL LAB	• Hematology • Chemistry • Serum pregnancy test[c]	• Urinalysis[d] • aPTT/PT/INR • BNP[b]
CENTRAL LAB	• Blood tests[b] • Archival Tumor Samples or Fresh Biopsy Block/Slides[e]	• Urinalysis
IRT	• Register subject information and screening visit	• Randomization/Drug Assignment[f]

NOTES:

Abbreviations: aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; IRT = Interactive Response Technology; INR = international normalized ratio; MRI = magnetic resonance imaging; PT = prothrombin time

a. Subject weight will be assessed prior to dosing at all study drug dosing visits; height will be assessed at Screening only.

b. Blood tests include hematology, chemistry, aPTT/PT/INR, BNP and CEA tests. Local BNP result may be substituted by the central lab BNP result for eligibility if the site local lab cannot perform the BNP test (allow sufficient time for central lab processing).

c. For women of childbearing potential, a serum pregnancy test will be performed at Screening.
d. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.
e. Tumor tissue (most recent archival sample or fresh biopsy) must be confirmed available prior to enrollment. Only one type of tissue is required during screening: archival tissue (formalin-fixed paraffin-embedded [FFPE]) or fresh biopsy (FFPE per Institutional standards). The tumor sample can be sent as a FFPE block or freshly cut unstained slides (refer to laboratory manual for details).
f. Randomization may occur up to 3 days prior to Cycle 1 Day 1; however, randomization on Cycle 1 Day 1 is preferred. If randomization occurred more than 3 days prior to Cycle 1 Day 1, sponsor must be notified. Subject who is randomized and then voluntarily declines study participation prior to dosing on C1D1 cannot be randomized again.

The Investigator or designee will review screening laboratory results, medical and cancer therapy history and screening radiographic reports and complete the eligibility checklist. Subjects who meet the eligibility criteria will be enrolled and randomized for drug assignment on the study. Subjects will not be enrolled/randomized in the study if laboratory or other screening results are not acceptable or missing.

Cycle 1, DAY 1:

INTERVIEW	• Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG) • Medical and Cancer History
EXAM	• Physical Exam (limited)[a]	• Vital Signs (BP measured in triplicate) (pre-dose and 30 to 45 minutes post-dose)
LOCAL LAB	• Hematology[b] • Chemistry[b]	• Urinalysis[b,c] • Serum pregnancy test[d]
CENTRAL LAB (Pre-dose)	• Blood tests[b,f] • Urinalysis[b] • PK Samples • Pharmacogenetic Whole Blood Sample (DNA) (Optional)[e]	• ADA/nAb Samples • Biomarker Plasma Sample • Biomarker Whole Blood Sample
TREATMENT	• Administer Study Drug (ABT-165 or bevacizumab)	• Administer FOLFIRI
CENTRAL LAB (Post-dose)	• PK Sample (within 30 mins)	

NOTES:
Abbreviations: ADA = antidrug antibody; BP = blood pressure; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; nAb = neutralization effect of the ADA; PK = pharmacokinetic

a. Subject weight will be assessed prior to dosing at all study dosing visits.

b. Only if screening labs are > 14 days from Cycle 1 Day 1, then local labs (chemistry, hematology and urinalysis) and central laboratory tests must be performed and assessed prior to first dose.
c. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.
d. For women of childbearing potential, a urine or serum pregnancy test will be performed up to 3 days prior to Cycle 1 Day 1. The pregnancy test results must be reviewed and determined to be negative prior to dosing with ABT-165/bevacizumab.
e. An optional pharmacogenetic sample (DNA) may be collected pre-dose from subjects who consent.
f. Blood tests include hematology and chemistry tests.

Cycle 1, DAY 8:

(± 2 days)

INTERVIEW	• Adverse Event Assessment	• Prior/Concomitant Therapy
EXAM	• Physical Exam (limited)	• Vital Signs (BP measured in triplicate)
LOCAL LAB	• Hematology	• Chemistry
CENTRAL LAB	• Blood tests[a]	

NOTES:
Abbreviation: BP = blood pressure
a. Blood tests include hematology and chemistry tests.

Cycle 2, DAY 1:

(± 2 days)

INTERVIEW	• Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG)
EXAM	• Physical Exam (limited)[a]	• Vital Signs (BP measured in triplicate) (pre-dose and 30 to 45 minutes post-dose)
LOCAL LAB	• Hematology[b] • Chemistry[b]	• Urinalysis[b,c]
CENTRAL LAB (Pre-dose)	• Blood tests[b,d] • Urinalysis[b]	• Biomarker Plasma Sample • Biomarker Whole Blood Sample
TREATMENT	• Administer Study Drug (ABT-165 or bevacizumab)	• Administer FOLFIRI

NOTES:
Abbreviations: BP = blood pressure; ECOG = Eastern Cooperative Oncology Group

a. Subject weight will be assessed prior to dosing at all study dosing visits.
b. Chemistry, hematology, urinalysis, and central laboratory tests may be obtained up to 3 days prior to Day 1 at Cycle 2 and beyond.
c. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.
d. Blood tests include hematology and chemistry tests.

Cycle 2, DAY 8:

(± 2 days)

INTERVIEW	• Adverse Event Assessment	• Prior/Concomitant Therapy
EXAM	• Physical Exam (limited)	• Vital Signs (BP measured in triplicate)
LOCAL LAB	• Hematology	• Chemistry
CENTRAL LAB	• Blood tests[a]	

NOTES:
Abbreviation: BP = blood pressure

a. Blood tests include hematology and chemistry tests.

Cycle 3, DAY 1:

(± 2 days)

INTERVIEW	• Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG)
EXAM	• Physical Exam (limited)[a]	• Vital Signs (BP measured in triplicate) (pre-dose and 30 to 45 minutes post-dose)
LOCAL LAB	• Hematology[b] • Chemistry[b]	• Urinalysis[b,c] • Serum or urine pregnancy test[d]
CENTRAL LAB (Pre-dose)	• Blood tests[b,f] • Urinalysis[b] • PK Samples • ADA/ nAb Samples • Biomarker Plasma Sample	• Biomarker Whole Blood Sample • Pharmacogenetic Whole Blood Sample (DNA) (Optional)[e]
TREATMENT	• Administer Study Drug (ABT-165 or bevacizumab)	• Administer FOLFIRI
CENTRAL LAB (Post-dose)	• PK Sample (within 30 mins)	

NOTES:

Abbreviations: ADA = antidrug antibody; BP = blood pressure; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; nAb = neutralization effect of the ADA; PK = pharmacokinetic

a. Subject weight will be assessed prior to dosing at all study dosing visits.

b. Chemistry, hematology, urinalysis, and central laboratory tests may be obtained up to 3 days prior to Day 1 at Cycle 2 and beyond.

c. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.

d. For women of childbearing potential, a urine or serum pregnancy test will be performed up to 3 days prior to Day 1 of every odd dosing cycle. The pregnancy test results must be reviewed and determined to be negative prior to dosing with ABT-165/bevacizumab.

e. An optional pharmacogenetic sample (DNA) may be collected pre-dose from subjects who consent.

f. Blood tests include hematology, chemistry, BNP and CEA tests.

Cycle ≥ 4, DAY 1:

(–2 days to +5 days)

INTERVIEW	• Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG)
EXAM	• Physical Exam (limited)[a]	• Vital Signs (BP measured in triplicate) (pre-dose and 30 to 45 minutes post-dose)
LOCAL LAB	• Hematology[b] • Chemistry[b]	• Urinalysis[b,c] • Serum or urine pregnancy test[d] (at odd cycles only)
CENTRAL LAB (Pre-dose)	• Blood tests[b,e] • Urinalysis[b] • PK Samples (Cycle 7, 11, 15 and 19)	• ADA/nAb Samples (Cycle 7, 11, 15 and 19) • Biomarker Plasma Sample (Cycle 8 only)
TREATMENT	• Administer Study Drug (ABT-165 or bevacizumab)	• Administer FOLFIRI
CENTRAL LAB (Post-dose)	• PK Sample (within 30 mins at Cycle 7, 11, 15 and 19)	

NOTES:

Abbreviations: ADA = antidrug antibody; BP = blood pressure; ECOG = Eastern Cooperative Oncology Group; nAb = neutralization effect of the ADA; PK = pharmacokinetic

a. Subject weight will be assessed prior to dosing at all study dosing visits.

b. Chemistry, hematology, urinalysis, and central laboratory tests may be obtained up to 3 days prior to Day 1 at Cycle 2 and beyond.

c. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.

d. For women of childbearing potential, a urine or serum pregnancy test will be performed up to 3 days prior to Day 1 of every odd dosing cycle. The pregnancy test results must be reviewed and determined to be negative prior to dosing with ABT-165/bevacizumab.

e. Blood tests include hematology, chemistry, BNP (odd cycles) and CEA (odd cycles) tests.

Every 8 weeks from Cycle 1 Day 1:

(± 1 week)

EXAM	• Cardiac ECHO • 12-lead ECG	• Tumor Assessment (CT Scan/MRI)[a]

NOTES:

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; MRI = magnetic resonance imaging

a. Post-baseline tumor assessment (both by blinded independent central review and by investigator assessment) will be conducted every 8 weeks from Cycle 1 Day 1 until radiographic progression. Scheduled tumor assessments will not be affected by delays in therapy. Tumor assessments should be conducted prior to the start of the next scheduled cycle of study treatment. An unscheduled tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression and no scan has been performed within the last 4 weeks. Radiographic RECIST progression should be documented when possible. The same imaging technique should be used throughout the study if possible.

Final Visit:

(30 [± 15] days after last dose)

INTERVIEW	• Adverse Event Assessment • Prior/Concomitant Therapy	• Performance Status (ECOG)
EXAM	• Physical Exam (limited) • 12-lead ECG	• Vital Signs (BP measured in triplicate) • Tumor Assessment (CT Scan/MRI)[a]
LOCAL LAB	• Hematology • Chemistry	• Urinalysis[b] • Serum or urine pregnancy test[c]
CENTRAL LAB	• Blood tests[e] • Urinalysis • PK Samples	• ADA/nAb Samples • Biomarker Plasma Sample • Tumor Biopsy at Progression (Optional)[d]

NOTES:

Abbreviations: ADA = antidrug antibody; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; nAb = neutralization effect of the ADA; PK = pharmacokinetic

a. A tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression and no scan has been performed within the last 4 weeks.

b. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection.

c. For women of childbearing potential, a urine or serum pregnancy test will be performed at final visit.

d. An optional tumor biopsy at time of disease progression may be obtained from subjects who consent voluntarily and if it is deemed safe to do so by the Investigator.
e. Blood tests include hematology, chemistry, BNP and CEA tests.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

Follow-Up (every 90 [± 15] days[a]):

INTERVIEW	• Adverse Event Assessment[b] • Post-treatment Cancer Information	• Date and Cause of Death
LOCAL LAB	• Serum or urine pregnancy test[c]	

NOTES:
a. Starting 90 (± 15) days after the last dose of study drugs, a follow-up every 90 days (± 15) or as required for data analysis will be performed for subject's survival information and post-treatment cancer information. Follow-up may continue for up to 2 years from the last dose of study drug or until the endpoint of death via subject contact, phone call or medical chart review as appropriate.
b. Adverse event assessment will be performed for up to 90 days after the last dose of study drug unless another anti-cancer therapy has been started.
c. For women of childbearing potential, a urine or serum pregnancy test will be performed monthly for approximately 6 months after the last dose of study drug.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the

subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Samples for optional pharmacogenetic analyses will only be collected if the subject has voluntarily signed and dated a separate written consent form for pharmacogenetic testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

3.2 Medical/Cancer History

A complete medical history including history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment. A detailed oncology history will also be collected including: histology, date of diagnosis of metastatic colorectal cancer (mCRC), stage and grade of mCRC, RAS status, primary tumor location, any surgical procedures, treatments administered (including dates and type of modality), and any other cancers besides mCRC.

On Cycle 1 Day 1, any additional medical history observed after signing of the informed consent but prior to initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

3.3 Adverse Event Assessment

Please refer to Section 4.2 on page 23.

3.4 Pharmacokinetic Sampling

Blood samples for subjects on both arms will be collected for analysis of serum concentrations. Blood samples will be collected throughout the treatment period on the study and the time points specified in Table 1, and processed as outlined in the most current version of the Study M14-064 laboratory manual.

Serum concentrations of ABT-165, the presence of antidrug antibodies (ADA) and, as needed, the neutralization effect of the ADA (nAb), will be determined using validated methods by or under supervision of the bioanalysis department at AbbVie. Serum samples collected for ABT-165 and ABT-165

ADA analysis may be used for future assay development or validation activities. Testing for serum samples collected for bevacizumab may be performed as needed.

3.5 Biomarker Research Sampling

Biomarker samples for subjects on both arms will be collected throughout the treatment period on the study and the time points specified in Table 1, and processed as outlined in the most current version of the Study M14-064 laboratory manual.

Exploratory biomarker assessments may include (but are not limited to) pathway(s) targeted by ABT-165 and those believed to be related to colorectal cancer, the disease being studied. The types of biomarkers studied may include nucleic acids, proteins, lipids, or metabolites. Samples may also be used to develop new diagnostic tests, therapies, research methods, or technologies. The analyses are exploratory in nature, may be conducted in non-Good Laboratory Practice (GLP) laboratories, and the results may not be included with the clinical study report. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. Biomarker samples may be stored for up to 20 years, while research on ABT-165 (or drugs of this class) or colorectal cancer and related conditions continues.

Blood Samples

Peripheral blood samples may be collected to conduct exploratory analyses to identify potential prognostic, predictive, or surrogate biomarker signatures, including (but not limited to) the following:

- Circulating nucleic acids in the peripheral blood may be analyzed at baseline and subsequent time points on therapy to assess tumor-related genetic alterations and to determine the effect of therapy.
- Expression levels (ribonucleic acid [RNA] or protein) of molecules may be assessed (e.g., molecules involved in the angiogenesis pathway) and evaluated for correlations with efficacy.

Tumor Tissue Collection

Archived or Fresh Tissue Biopsy. All subjects should provide a tumor sample prior to enrollment in the study. Availability of archival tissue (most recent sample is preferred) needs to be confirmed prior to enrollment in the study. If no archived tissue is available, a fresh pre-treatment biopsy should be collected from subjects as per Institutional guidelines, if it is deemed safe to do so in the judgment of the Investigator.

Pharmacogenetic deoxyribonucleic acid (DNA) Sample (Optional)

Whole blood samples for pharmacogenetic exploratory research (DNA) will be collected from subjects who consent. DNA samples may be analyzed for genetic factors contributing to the subject's response to ABT-165, or other study treatment, in terms of pharmacokinetics (PK), pharmacodynamics, efficacy, tolerability, and safety. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ABT-165 or drugs of this class.

Table 1. Schedule of Study M14-064 Study PK and Biomarker Samples (for Subjects on Both Arms)

Samples	Time Point	Volume	Screening (Up to 28 Days Before Randomization)	Cycle 1, Day 1	Cycle 2, Day 1 (± 2 Days)	Cycle 3, Day 1 (± 2 Days)	Every 4 Cycles, Day 1 (Cycle 7, 11, 15, 19) (–2 Days to +5 Days)	Final Visit (± 15 Days)
MANDATORY PERIPHERAL BLOOD & TISSUE COLLECTIONS								
PK Sample	Pre-dose and within 30 min (± 10 min) post-infusion	2 mL		✓		✓	✓	✓
ADA/nAb Sample	Pre-dose	3 mL		✓		✓	✓	✓
Biomarker Plasma Sample	Pre-dose	5 mL		✓	✓	✓	Cycle 8, Day 1 ONLY	✓
Biomarker Whole Blood Sample	Pre-dose	2.5 mL		✓	✓	✓		
Archival Tumor Samples or Fresh Biopsy	Screening	Block/ Slides	✓					
OPTIONAL PERIPHERAL BLOOD & TISSUE COLLECTIONS								
Tumor Biopsy at Progression	At disease progression	Block/ Slides						✓
Pharmacogenetic Whole Blood (DNA)	Pre-dose	4 mL		✓		✓		

Abbreviations: ADA = antidrug antibody; DNA = deoxyribonucleic acid; nAb = neutralization effect of the ADA; PK = pharmacokinetic

3.6 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the designated study visits as specified in Section 2.1. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

3.7 Cardiac ECHO

Echocardiogram (ECHO) will be performed at screening and approximately every 8 weeks from Cycle 1 Day 1 as specified in Section 2.1. It is preferred that the same operator, machine and calculation algorithm be used throughout the course of the study.

At Screening, ECHO will be performed to determine if any findings outside normal physiological variation are clinically significant, including but not limited to left ventricular ejection fraction and peak tricuspid velocity. Any clinically significant findings outside normal physiological variation will be documented on the appropriate electronic case report form (eCRF). For subsequent ECHOs performed every 4 cycles, any significant changes from baseline or evaluations performed while on study should be documented. Any clinically significant changes, including pulmonary hypertension and decrease in left ventricular ejection fraction, from baseline will be evaluated by the Investigator and Medical Monitor prior to further dosing.

The assessment performed at Screening will serve as the baseline for future comparisons. Additional cardiac assessments and studies may be performed at the discretion of the Investigator after consultation with the Medical Monitor.

All study reports will be retained as source documentation in the subject's records at the study site. Any abnormal study reports, including the screening reports, in subjects who have been dosed with ABT-165 will be forwarded to the Sponsor for further evaluation. The Sponsor may also choose to have ECHO

scans/reports reviewed by an independent central radiographic institution at any time during or after the study.

3.8 Height and Weight

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing. Ideal, total or adjusted weight will not be used.

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in triplicate, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1.

In general, blood pressure (BP) measurements should follow the most current guidelines of the American Heart Association with the following considerations. Blood pressure and heart rate measurements should be performed prior to scheduled blood collections. At each office visit, BP will be measured in triplicate approximately 5 minutes apart. Blood pressure and pulse rate will be measured after the subject has been sitting comfortably in a chair with legs uncrossed and back supported. The arm used for BP measurements should be supported for at least 5 minutes. Triplicate BP measurements may be repeated if there were any disruptions during the measurements (i.e., blood draws, exams etc.) or if Investigator/Staff consider BP readings are not accurate due to anxiety (i.e., "white coat hypertension") or other issues unrelated to study drug.

Home Blood Pressure Monitoring

Since hypertension is expected, the Sponsor will provide each subject with a BP monitor capable of recording BPs for the duration of the subject's participation in the study. The subject (or their caretaker) will measure the subject's BP daily (or more often if needed to manage hypertension), starting after dosing on Cycle 1 Day 1 and lasting to the end of Cycle 2. Subjects and/or their caretakers will be trained on the proper methods to measure BP at home and will be instructed to contact the Investigator/Site Staff for management of BP readings ≥ 160/100. Beginning with Cycle 3, subjects with well controlled hypertension as assessed by the Investigator, may measure their BP at home less frequently (approximately 3 times/week) but should still be instructed to contact Investigator/Site Staff for management of BP readings ≥ 160/100.

Subjects will be instructed to bring their home monitoring equipment and diary with them to each clinic visit. Data from home BP monitoring may be used to adjust antihypertensive medications in between clinic visits as needed to maintain the majority of BPs < 150/90.

3.10 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as adverse events (AEs). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

3.11 Administration of Study Drugs

Study drug will be administered to subjects as specified in Section 2.1. The first dose of study drug will be administered after all other baseline (Day 1) procedures are completed.

ABT-165 or bevacizumab will be administered as an intravenous (IV) infusion on Day 1 of every 14-day dosing cycle. Blood pressure will be measured in triplicate prior to each dose of ABT-165/bevazicumab and if all three measurements have either systolic ≥ 150 or diastolic ≥ 90 mmHg (either systolic or diastolic exceeded on all 3 readings), the subject cannot receive the dose of ABT-165/bevacizumab.

The dose of ABT-165/bevacizumab does not need to be adjusted unless the subject's measured weight changes by > 10% from baseline. Site standard of care for bevacizumab dosing will supersede guidelines given in this protocol.

Subjects will not be pre-medicated for prophylaxis of infusion-related reactions (IRRs) prior to the first infusion of ABT-165/bevacizumab. The first dose of ABT-165/bevacizumab will be given intravenously over 60 ± 10 minutes. Subjects will be closely monitored for IRRs (chills, fever, rigors, hypertension, rash or other acute toxicities) during the infusion and the post-infusion observation period (30 – 45 minutes). If the first infusion is tolerated, the second and subsequent infusions of ABT-165/bevacizumab may be administered over 30 ± 10 minutes provided that subjects have not experienced IRRs. For those subjects who required a 90 minute infusion of bevacizumab in the first-line setting, the first infusion of ABT-165 or bevacizumab will be administered over 90 (± 10) minutes and may be decreased to 60 (± 10) minutes and 30 (± 10) minutes as tolerated. Subjects who had a history of infusion reactions with bevacizumab may be premedicated to prophylax IRRs at the discretion of the Investigator if they are receiving bevacizumab or ABT-165.

After the first infusion, direct observation is not required; however, pre-infusion and post-infusion (30 to 45 minutes) vital signs should still be taken. Longer observation periods and more frequent vital sign checks may be required in subjects who experience IRRs or elevations in BP. Subjects who experience acute elevations of BP during or in the observation period following a dose, should be monitored in

clinic until BP is < 150/90 mmHg for at least 1 hour with or without medication after which time they may be monitored and treated in the outpatient setting as medically appropriate.

For subjects experiencing an acute IRR, immediately interrupt ABT-165/bevacizumab infusion and administer appropriate medical therapy such as acetaminophen/paracetamol, diphenhydramine, H2-blockers, or steroids per Institutional standard of care. Subjects who have had a Grade 1 or 2 IRR may be treated prophylactically prior to subsequent doses at the Investigator's discretion.

Folinic acid, fluorouracil, and irinotecan (FOLFIRI) will be administered per Institutional guidelines and best medical practice (Protocol suggested dosing guidelines are given below). Modifications of FOLFIRI therapy, both the initial dose (depending on tolerance of prior therapy) and subsequent doses, are allowed at the discretion of the Investigator following prescribing information, Institutional guidelines, or best medical practice. Subjects receiving ABT-165/bevacizumab and FOLFIRI should receive full supportive care including any standard pre-medications and monitoring associated with administration of Standard of Care agents. Any toxicity associated with FOLFIRI should be managed utilizing best medical practice which may include symptomatic treatment and/or reduction or modification of FOLFIRI therapy.

Administration of Irinotecan

For the purposes of this protocol, the suggested dosing of irinotecan is 180 mg/m^2 administered as a 90 (± 15) minute IV infusion on Day 1 of each 14-day cycle. Investigators should evaluate subjects for irinotecan treatment per the locally approved product label, local practice, or applicable Summary of Product Characteristics (SmPC).

Administration of Leucovorin (LV; folinic acid)

For the purposes of this protocol, the suggested dosing of leucovorin is DL-400 mg/m^2 or L-200 mg/m^2 administered as a 90 (± 15) minute IV infusion concurrent with irinotecan on Day 1 of each 14-day cycle. Irinotecan and leucovorin may be administered sequentially in accordance with local practice. Investigators should evaluate subjects for leucovorin treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Fluorouracil (5-FU) Bolus

For the purposes of this protocol, a suggested 5-FU 400 mg/m^2 bolus (up to 15 minutes) will be administered followed by the 5-FU infusion. Investigators should evaluate subjects for 5-FU treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Fluorouracil (5-FU) Infusion

For the purposes of this protocol, the suggested dosing of 5-FU is 2400 mg/m^2 administered as a 46-hour (± 2 hours) IV infusion on Day 1 of each 14-day cycle. Investigators should evaluate subjects for 5-FU treatment per the locally approved product label, local practice, or applicable SmPC.

At the discretion of the Investigator, the 5-FU bolus or continuous infusion may be reduced or eliminated depending on the subject's tolerability of prior treatment.

Order of Administration

Protocol therapy will be administered in the following order: ABT-165/bevacizumab **followed by** FOLFIRI as irinotecan **concurrent with** leucovorin **followed by** a 5-FU bolus **followed by** 5-FU infusion. For the purposes of this protocol, ABT-165/bevacizumab should always be given first.

Irinotecan and leucovorin may be administered sequentially in accordance with local treatment practice.

3.12 Tumor Assessments

Baseline radiographic tumor assessment must be performed within 28 days prior to Cycle 1 Day 1 and will consist of computed tomography (CT) (or magnetic resonance imaging [MRI] where clinically indicated) of the chest, abdomen, and pelvis (and other tumor involved regions as clinically indicated). Imaging will be repeated every 8 weeks from Cycle 1 Day 1. Imaging will also be performed at the Final Visit if a subject discontinues from the study for a reason other than radiographic progression and no scan has been performed within the last 4 weeks. Imaging may also be performed at other times if the Investigator suspects tumor progression. Imaging of the brain for metastatic disease will only be performed if clinically indicated. The same imaging technique should be used throughout the study if possible. The tumor assessment performed at Screening will serve as the baseline for clinical assessment. Changes in measurable lesions over the course of therapy will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as described in Appendix B. Radiographic images will be evaluated both by the site and by a blinded, independent central radiographic institution.

3.13 Clinical Laboratory Tests

All subjects will have laboratory analyses performed as outlined in Table 2. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. A local reference laboratory will perform chemistry, hematology, coagulation, and urinalysis tests for subject treatment

management and eligibility; however, split or concurrent samples *must* be drawn and sent to the central laboratory for analysis (applies to scheduled and unscheduled labs).

The Central laboratory tests may include hematology, chemistry, urinalysis, coagulation, carcinoembryonic antigen (CEA), or brain natriuretic peptide (BNP) depending on the study visit. Central laboratory chemistry, hematology, coagulation, and urinalysis tests will be performed at the same study visit as the local laboratory tests. Central laboratory BNP and CEA will be performed at odd numbered study visits and at the final study visit. The central laboratory data will be used for safety analysis and any other related analysis.

If there is a discrepancy between the local and central laboratory results, the site must enter the relevant local laboratory results that were used for eligibility or treatment decisions on the appropriate eCRF along with reference ranges.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the following certified laboratory addresses depending on the location of the site:

COVANCE CENTRAL LABORATORY SERVICES L.P.
8211 SciCor Drive
Indianapolis, IN
46214-2985 USA
Tel (317) 271 1200 (local calls)
Fax (317) 273 4030

COVANCE CENTRAL LABORATORY SERVICES SÀRL
Rue Moïse-Marcinhes 7
CH - 1217 Meyrin/Genève
Switzerland
Tel +41 58 822 7901
Fax +41 58 822 7521

Covance (Asia) Pte. Limited
1, International Business Park
#01-01 The Synergy
Singapore 609917
Tel +65 6560 8793
Fax +65 6565 5901

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value if needed;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE.

Table 2. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Coagulation Tests**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Albumin Alanine transaminase (SGPT/ALT) Aspartate transaminase (SGOT/AST) Gamma-Glutamyl Transferase (GGT) Alkaline phosphatase**** Sodium Potassium Calcium Inorganic phosphorus**** Uric acid**** Cholesterol**** Total protein Glucose Triglycerides**** Lactate dehydrogenase (LDH) **** Magnesium**** Bicarbonate/CO_2 Chloride Creatinine clearance	Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ratio (INR)
		Cardiac
		BNP
Urinalysis		**Tumor Marker**
Specific gravity Ketones pH Protein* Blood Glucose		Carcinoembryonic antigen (CEA)**
		Pregnancy Tests Serum or Urine
		*Human Chorionic Gonadotropin (hCG)****

* For proteinuria of ≥ 2+, confirm total urine protein with a 24-hour urine collection.

** CEA tests will be performed at the central laboratory. Sites may do their own CEA testing but should not discontinue subjects based on rising CEA alone unless clinically warranted.

*** At Screening and at any time point in which pregnancy is suspected or following a positive urine pregnancy test.

**** Optional local laboratory tests

Pregnancy Tests (Serum and Urine)

A serum pregnancy test will be performed at Screening and a serum or quantitative urine pregnancy test will be performed monthly on Study Day 1 of each odd treatment cycle for all women of child-bearing potential (WOCBP) subjects.

If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated 2 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Still borderline, the AbbVie Therapeutic Area Medical Director will be consulted.

Determination of postmenopausal status will be made during the screening period based on the subject's history.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Additional urine pregnancy tests will be performed at visits indicated in Section 2.1.

If the urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.

Monthly pregnancy tests will be continued after the last treatment cycle for 6 months for all WOCBP subjects.

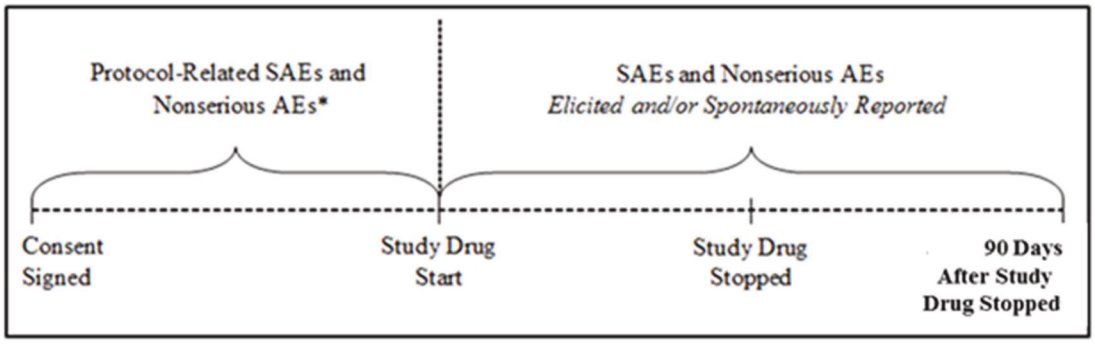
Chemistry

No fasting is required for the collection of blood samples for serum chemistry tests.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All protocol-related serious adverse events (SAEs) as well as nonserious AEs will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 90 days after discontinuation of study drug administration or start of another anti-cancer therapy, whichever occurs sooner, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject.



* Only if considered by the investigator to be causally related to study required procedures.

4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 90 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment emergent adverse events by severity grade and relationship to study drug will also be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within a SOC will be counted only once for that SOC.

Safety data will be monitored by the Sponsor and documented internally. Throughout study conduct for Study M14-064, individual subject safety data and aggregate safety data will be reviewed by the Safety Management Team, the Therapeutic Area Medical Director and the Product Safety Team Therapeutic Area Physician with potential safety signals assessed by a cross functional ABT-165 Product Safety Team. As part of routine pharmacovigilance, individual case safety reports are reviewed per timelines for regulatory reporting and aggregate safety data reviewed on a quarterly basis by the previously referenced AbbVie personnel. Within this context, critical safety related data points such as AEs, vital signs and laboratory data will be reviewed on an ongoing basis in accordance with the Study M14-064 safety review plan (SRP). Annually, in conjunction with the update of the Investigator Brochure, an aggregate review of the safety data across all study cohorts will be conducted and will include frequencies of treatment-emergent serious adverse events (SAEs) and non-serious AEs by MedDRA SOC and PT tables, deaths, SAEs, and AEs of special interest. Sites will be informed of any significant findings impacting subject safety as they arise.

An internal Data Monitoring Committee (DMC) comprised of persons independent of the AbbVie study team and with relevant expertise in their field will be established to review unblinded safety data

initially approximately 6 months after the first subject is enrolled and approximately every 3 months thereafter. Furthermore, the DMC will also review the available efficacy data approximately every 3 months.

4.3 Definition of Adverse Event

An AE can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of an AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specified criteria (see Section 6.2 in protocol regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known), or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drug, the investigator will assign "other" as the cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be recorded.

All AEs will be followed to a satisfactory conclusion.

Disease progression and signs, symptoms or test abnormalities that, in the opinion of the investigator, are unequivocally due to disease progression should not be reported as AEs, even if serious or fatal (see also Section 4.4 and Section 4.5).

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was preplanned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. Hospitalization of a subject who is in Post Treatment Follow-Up or Survival, following discontinuation of study drug, for subsequent line of therapy will not be captured as an SAE. A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of study drug is administered until 90 days have elapsed following discontinuation of study drug administration.

4.4 Adverse Events Commonly Associated with mCRC Study Population and/or Progression of mCRC

Certain AEs are anticipated to occur in the study population at some frequency independent of drug exposure. Such events include known consequences of mCRC (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population).

These AEs may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

4.5 Adverse Events Expected Due to Study-Related Endpoints

Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of mCRC should be recorded only on the study completion eCRF with disease progression as the reason for discontinuation and not on the AE eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only 1 such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death because of presumed cardiac causes in a subject with or without pre-existing heart disease within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. During survival follow-up, deaths attributed to progression of mCRC should be recorded only on the survival eCRF.

Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease, including transformation to a more aggressive histology, are also considered an expected outcome for this study and will NOT be recorded as AEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, the event should be reported as an AE.

4.6 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [redacted]
FAX to: [redacted]

For safety concerns, contact the Oncology Safety Team at:

Oncology Safety Team [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office: [redacted]
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
Senior Medical Director, Oncology
1500 Seaport Blvd.
Redwood City, CA 94063

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the European Union countries will be the most current version of the Investigator's Brochure.

5 STUDY DRUG

5.1 Treatments Administered

The study drug (ABT-165), comparator (bevacizumab), and back-bone (irinotecan, leucovorin, and 5-FU) will be dispensed in the form of an IV infusion at the visits listed in Section 2.1.

ABT-165 will be provided by AbbVie as lyophilized powder in vials containing 200 mg each. For bevacizumab, irinotecan, leucovorin, and 5-FU refer to country-approved package insert or SmPC.

ABT-165 (2.5 mg/kg or 1.25 mg/kg for the first 2 cycles, see below) or bevacizumab (5 mg/kg) with irinotecan (180 mg/m^2), leucovorin (DL-400 mg/m^2 or L-200 mg/ m^2), and 5-FU (bolus: 400 mg/m^2; then continuous infusion: 1200 mg/m^2/day × 2 days - total of 2400 mg/m^2 over 46 – 48 hours) will be administered intravenously on Day 1 of each 14-day cycle. The Investigator may adjust the suggested FOLFIRI dosing based on Institutional guidelines and best medical practice.

The starting dose of ABT-165 should be 1.25 mg/kg for first 2 cycles if the last dose of bevacizumab is within 6 weeks of ABT-165 treatment initiation. The dose of ABT-165 should then be increased to 2.5 mg/kg after 2 cycles of the 1.25 mg/kg dose.

Study drug must not be dispensed without contacting the Interactive Response Technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

If any planned study drug (ABT-165/bevacizumab or FOLFIRI) of a cycle is not given, site will register the information in IRT and EDC and indicate as "not given."

5.2 Packaging and Labeling

All study drugs will be supplied in vials.

Each vial will be labeled as required per country requirements.

The labels must remain affixed to the vials.

Storage and Disposition of Study Drug

ABT-165 and bevacizumab must be refrigerated (2 to 8°C) for storage. For irinotecan, leucovorin, and 5-FU refer to country-approved package insert or SmPC.

All temperature excursions lasting longer than 30 minutes must be reported to AbbVie. Study drug should be physically quarantined (status of drug in IRT should not be changed to "quarantined" unless instructed by the Sponsor study team). Study drug that has experienced a temperature excursion should not be dispensed until AbbVie (or temperature excursion management system) deems drug as acceptable.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, randomized, 2-arm study. All eligible subjects will receive ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan – 180 mg/m^2; leucovorin – DL-400 mg/m^2 or L-200 mg/m^2; 5-FU – bolus: 400 mg/m^2, infusion: 2400 mg/m^2) or bevacizumab (5 mg/kg) plus FOLFIRI on Day 1 of each 14-day cycle until disease progression or study discontinuation.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

5.4 Selection and Timing of Dose for Each Subject

During the randomization process, subjects will be randomized in a 1:1 ratio to either ABT-165 2.5 mg/kg IV plus FOLFIRI or bevacizumab 5 mg/kg IV plus FOLFIRI.

The starting dose of ABT-165 should be 1.25 mg/kg for first 2 cycles if the last dose of bevacizumab is within 6 weeks of ABT-165 treatment initiation. The dose of ABT-165 should then be increased to 2.5 mg/kg after 2 cycles of 1.25 mg/kg dose.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BP	Blood Pressure
BNP	Brain Natriuretic Peptide
BUN	Blood urea nitrogen
CEA	Carcinoembryonic Antigen
CR	Complete Response
CT	Computed Tomography
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
5-FU	Fluorouracil
FFPE	Formalin-Fixed Paraffin-Embedded
FOLFIRI	Folinic Acid, Fluorouracil, and Irinotecan
hCG	Human Chorionic Gonadotropin
IV	Intravenous
IEC	Independent ethics committee
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology

LDH	Lactate dehydrogenase
LV	Leucovorin
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRI	Magnetic Resonance Imaging
nAb	Neutralization effect of the ADA
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RPLS/PRES	Posterior Reversible Leukoencephalopathy Syndrome
SAE	Serious adverse event
SGPT	Alanine transaminase
SGOT	Aspartate transaminase
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
WOCBP	Women of Child-Bearing Potential
WBC	White Blood Cell

APPENDIX B. RECIST (VERSION 1.1) CRITERIA FOR TUMOR RESPONSE

Response criteria will be assessed using RECIST (version 1.1). Changes in the measurable lesions over the course of therapy must be evaluated using the criteria listed below.

Eligibility

Subjects with measurable disease at Baseline can have objective tumor response evaluated by RECIST criteria. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least 1 dimension with a minimum size of: • longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) • 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.

Special Considerations Regarding Lesion Measurability	Bone lesions Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable. Cystic lesions Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions. Lesions with prior local treatment Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Methods of Measurement

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at Baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after

baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie Medical Monitor.

For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at Baseline. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease:

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of diameters recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-Progressive Disease:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease:

Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Note: If the subject discontinues treatment for symptomatic deterioration, every effort should be made to document objective progression even after discontinuation of treatment.

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at Baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at Baseline.

If a new lesion is equivocal (i.e., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

In all cases, confirmation of response is not required.