Official Title: **A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RO5520985 (VANUCIZUMAB) PLUS FOLFOX VERSUS BEVACIZUMAB PLUS FOLFOX IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER**

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PROTOCOL

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PROTOCOL NUMBER:	BP29262
VERSION:	**5**
EUDRACT NUMBER:	2013-005108-32
IND NUMBER:	120910
TEST PRODUCT:	RO5520985
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Translational Medicine Leader	10-Feb-2016 08:25:43

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PROTOCOL SYNOPSIS

TITLE	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RO5520985 (VANUCIZUMAB) PLUS FOLFOX VERSUS BEVACIZUMAB PLUS FOLFOX IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER**
PROTOCOL NUMBER:	BP29262
VERSION:	**5**
EUDRACT NUMBER:	2013-005108-32
IND NUMBER:	120910
TEST PRODUCT:	RO5520985
CLINICAL PHASE	II
SPONSOR	F. Hoffmann-La Roche Ltd
INDICATION	Patients with metastatic nonresectable colorectal cancer, untreated for their metastatic disease
OBJECTIVES	**Primary** The primary objective of Study BP29262 is to estimate the efficacy of RO5520985 in combination with oxaliplatin, folinic acid, and 5 fluorouracil (mFOLFOX-6) vs. bevacizumab in combination with mFOLFOX-6, as measured by progression-free survival (PFS). **Secondary** • Evaluate the safety and tolerability of RO5520985 in combination with mFOLFOX-6 • Estimate the efficacy of RO5520985 in combination with mFOLFOX-6, as measured by overall survival, objective response rate, and duration of objective response • Characterize the pharmacokinetics of RO5520985 when combined with mFOLFOX-6 **Exploratory** • Assess levels of circulating angiogenic factors and circulating targets as potentially predictive markers, in conjunction with somatic mutations in circulating cell-free DNA • Assess potential response prediction markers of RO5520985 in blood and archival primary tumor tissue • Explore tumor growth kinetics • Characterize the PK of selected mFOLFOX-6 components when combined with RO5520985 • Explore additional parameters on tumor imaging

STUDY DESIGN

This is a Phase II multicenter, randomized, parallel arms, double-blind study of RO5520985 to evaluate the efficacy and safety of RO5520985 plus mFOLFOX-6 versus bevacizumab plus mFOLFOX-6 in patients previously untreated mCRC. The study consists of two parts: Part I (Safety Run-in) open label single arm and Part II (Randomization Phase) randomized, parallel arms, double-blind study.

Part I: Safety Run-in

The safety/tolerability of single agent RO5520985 has been investigated in Study BP28179, by which RO5520985 at 2000 mg Q2W was considered safe and recommended as dose for subsequent clinical development. However, the combination of RO5520985 with mFOLFOX-6 has not been previously studied clinically for safety. Therefore, during the open label safety run-in phase prior to the randomization part of the study (Part II) at least 6 eligible patients will be exposed to 2000 mg Q2W RO5520985 + mFOLFOX-6, in order to confirm the dose and schedule that will be used in the randomized part of this study (Part II). All patients in Part I will receive induction and maintenance therapy as described for patients in the experimental arm of Part II.

Treatment of the first 6 patients will be sequential i.e., there will be always at least 1 working day between the 1st RO5520985 administration of one enrolled patient and the 1st RO5520985 administration of the next enrolled patient.

Each site enrolling one of the first 6 patients in Part I needs to inform the Sponsor about the tolerability (based on the assessments being performed as per SoA) by e-mail. The e-mail needs to be send after the investigator or designee has seen the patient during the Visit on Day 2 of Cycle 1 reporting at least the observed AEs/SAEs between start of RO5520985 administration and the Visit on the next day (C1D2). Only after confirmation by the site that the 1st study drug administration was tolerated without any severe problems, the next patient can be treated. The Sponsor ensures that the site enrolling the subsequent patient will be informed latest on the evening prior to the scheduled treatment whether the patient can receive the 1st RO5520985 administration.

After at least 6 patients have been treated by at least two full cycles an Internal Monitoring Committee (IMC) will conduct a safety analysis prior to initiation of Part II. If safety signals arise from the review and depending on the nature of the safety signals, the IMC may recommend to enroll additional 6-12 patients at lower doses of RO5520985 in combination with mFOLFOX-6 before embarking onto Part II of the study at the adjusted dose. In case of unacceptable and/ or non-manageable toxicity of the combination, the IMC may decide to discontinue the study upon completion of Part I. The IMC will operate according to a prespecified safety charter outlined in a separate document.

Part II: Randomization Part

Upon completion of the safety run-in part with selection of

	the RP2D of RO5520985 in combination with mFOLFOX-6 by the IMC, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX-6 + RO5520985 (experimental arm) or mFOLFOX-6 + bevacizumab (control arm). Patients will prospectively be stratified by region (United States vs. Rest of World [RoW]) and number of metastatic sites (1 vs. >1). Study treatment consisting of induction and maintenance therapy will be given in cycles repeated every 14 days and will consist of: <u>Induction therapy</u> Up to 8 cycles of mFOLFOX-6 plus either bevacizumab or RO5520985. Patients may switch to maintenance therapy earlier if oxaliplatin cannot be tolerated. <u>Maintenance therapy</u> Following induction therapy, oxaliplatin administration will be discontinued and patients receive 5-FU/folinic acid plus either RO5520985 (experimental arm) or bevacizumab (control arm) as maintenance therapy for a maximum period of 24 months (calculated from start of maintenance therapy), if treatment is not stopped earlier due to disease progession, unacceptable toxicity, Investigator decision or consent withdrawal. If patients stop chemotherapy either in part or in whole, then they should continue on RO5520985 treatment or bevacizumab for a maximum of 24 months. Within Part II of the study, two interim analyses are planned after approximately 30 and 50 PFS events.
NUMBER OF PATIENTS	Part I (Safety Run-in): 6–18 patients Part II (Randomization): 190 patients
TARGET POPULATION	Adult patients with metastatic colorectal cancer who have not been previously treated with chemotherapy for metastatic disease and who are not candidates for potentially curative resection.
INCLUSION/EXCLUSION CRITERIA	**<u>Inclusion Criteria</u>** 1. Histologically or cytologically confirmed mCRC not amenable to potentially curative resection with at least one measurable metastatic lesion, as defined by RECIST v1.1 a) Representative tumor specimens in FFPE blocks (preferred) or slides must be available for central extended RAS mutational analysis testing 2. Signed written informed consent, obtained prior to any screening procedure 3. Age ≥ 18 years 4. ECOG (WHO) performance status of 0 or 1 5. Willing and able to comply with the protocol as judged by the Investigator 6. Adequate hematologic function a) Absolute neutrophil count (ANC) ≥ 2000 cells/μL (without G-CSF support within 2 weeks prior to randomization) b) Platelet count ≥ 100,000/μL (without transfusion

within 2 weeks prior to randomization)

c) Hemoglobin ≥ 9.0 g/dL

7. Adequate liver function
   a) AST and ALT ≤ 2.5 × upper limits of normal (ULN) or ≤ 5 x ULN in case of liver metastases
   b) Serum bilirubin ≤ 1.5× ULN (Patients with known Gilbert disease who have serum bilirubin level ≤ 3× ULN may be enrolled)
   c) Serum albumin ≥ 3.0 g/dL
8. Adequate coagulation function
   a) International normalized ratio (INR) ≤ 1.5 × ULN
   b) Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
9. Adequate renal function
   a) Creatinine clearance ≥ 50 mL/min/1.73 m^2 on the basis of the Cockroft–Gault formula
   b) Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hrs urine collection and must demonstrate ≤ 1 g of protein in 24 hrs
10. Adequate cardiovascular function
    a) NYHA stage ≤ 1
    b) Resting blood pressure systolic < 150 mmHg and diastolic < 100 mmHg (average of ≥ 3 readings on ≥ 2 sessions)
11. Recovery from all reversible adverse events of previous medical therapies to baseline or NCI CTCAE Grade 1, except for alopecia (any grade)
12. Negative serum or urine pregnancy test within 7 days prior to starting study treatment in premenopausal women and women < 2 years after the onset of menopause

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Any prior systemic therapy (including chemotherapy, antibody therapy, tyrosine kinase inhibitors, immunotherapy, hormonal therapy) before Day 1 of Cycle 1 for treatment of mCRC
   a) Patients who received prior systemic adjuvant therapy or radiotherapy for CRC are not excluded if the time interval from last administration of adjuvant therapy until disease progression is > 12 months
   b) Patients who received herbal therapy intended as anti-cancer therapy ≥ 2 weeks prior to Day 1 are not excluded
2. Malignancies other than CRC within 5 years prior to randomization, except for those with a minimal risk of metastasis or death, such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ

treated surgically with curative intent

3. **R**adiotherapy within 28 days **and abdominal/ pelvic radiotherapy within 60 days** prior to Day 1 of Cycle 1, except palliative radiotherapy to bone lesions within 7 days prior to Day 1 of Cycle 1
4. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to Day 1 of Cycle 1
5. Pregnant or lactating women
6. Known hypersensitivity reaction to any study medication (or excipients)
7. Any disorder that compromises the ability of the patient to provide written informed consent and/or to comply with study procedures
8. Symptomatic CNS metastases or carcinomatous meningitis: Asymptomatic patients must be clinically stable with regard to their CNS/meningeal metastatic involvement, have completed previous therapy (including radiation and / or surgery) at least 4 weeks prior to study drug administration, are not receiving steroid therapy or taper, and are not receiving anti-convulsive medication for any CNS involvement
9. Active infection requiring IV antibiotics
10. Active autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of $\leq$ 10 mg/day prednisone
11. Sensory peripheral neuropathy $\geq$ Grade 2
12. Women of childbearing potential and men unwilling to practice an effective method of birth control from screening until 6 months after discontinuing study treatment. Childbearing potential is defined as sexually mature women who have not undergone a hysterectomy, have not been naturally post menopausal for at least 23 consecutive months or have a serum FSH $<$ 40 mIU/mL. Effective methods of birth control are defined as surgical sterilization [e.g., bilateral tubal ligation, vasectomy], hormonal contraception [implantable, patch, oral], or double-barrier methods [any double combination of: intrauterine device, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap]), or abstinence from intercourse. Abstinence as a method of contraception is only acceptable as “true abstinence”, i.e. when it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
13. Significant cardiovascular or cerebrovascular disease within 6 months prior to Day 1 of Cycle 1, including any of the following:
    a) Prior history of hypertensive crisis or hypertensive encephalopathy
    b) TIA,PRIND or stroke
    c) History of acute coronary syndromes (including acute myocardial infarction, unstable angina,

CABG, coronary angioplasty, or stenting)

d) Aortic aneurysm requiring surgical repair

e) Peripheral arterial thrombosis/thromboembolism

14. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
15. Current use of anticoagulants (e.g., warfarin or any other coumadin-derivate coagulants) at therapeutic doses within 7 days prior to study drug administration. Prophylactic use of unfractioned heparin or low molecular weight heparin (LMWH) is permitted (e.g., enoxaparin 40 mg QD)
16. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 **of Cycle 1**, or **abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to Day 1 of Cycle 1 or** anticipation of need for major surgical procedure during the course of the study or nonrecovery from side effects of any such procedure
17. **History of intra-abdominal inflammatory process within 6 months prior to Day 1 of Cycle 1, including but not limited to peptic ulcer disease, diverticulitis, or colitis**
18. **Colonic prosthesis (stent) implant in place**
19. History of abdominal or tracheo-oesophageal fistula or GI perforation or intra-abdominal abscess within 6 months prior to Day 1
20. **History of intestinal obstruction and/or clinical** signs or symptoms of GI obstruction **including sub-occlusive disease related to the underlying disease** or a requirement for routine parenteral hydration, parenteral nutrition, or tube feeding **within 6 months prior to Day 1 of Cycle 1. Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution**
21. **Chronic daily treatment with NSAID (occasional use for the symptomatic relief of medical conditions, e.g. headache or fever is allowed)**
22. **Chronic daily treatment with corticosteroids (dose > 10 mg/day methylprednisolone equivalent) excluding inhaled steroids**
23. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
24. Metastatic disease that involve major airways or blood vessels, or centrally located mediastinal tumor masses ($<$30 mm from the carina) of large volume
25. History of bronchopulmonary hemorrhage NCI CTCAE $\geq$ Grade 2 or gross hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to randomization
26. Severe, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture
27. Known dihydropyrimidine dehydrogenase deficiency or thymidylate synthase gene polymorphism predisposing the

patient for 5-FU toxicity

28. Any other condition, diseases, metabolic dysfunction (e.g., uncontrolled diabetes mellitus), active or uncontrolled infections/inflammation, physical examination finding, mental status or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates patients participation in the clinical study due to safety concerns, compliance with clinical study procedures or that may affect the interpretation of the results

LENGTH OF STUDY

The time needed for for study enrollment is estimated to be approximately 15 months. The total duration of the study for each patient will be as follows:

- Screening: Up to 4 weeks
- Treatment period: Patients will receive induction therapy for up to 8 cycles (approximately 4 months), followed by maintenance therapy for a maximum of 24 months unless the occurrence of disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision require treatment cessation.
- EoS Visit: Up to 6 weeks (5 ± 1 weeks) after last dose of RO5520985
- Post study HAHA Visit (optional): 2 months (± 14 days) after last dose of RO5520985
- Post study follow-up: All patients will be followed for survival (e.g., by phone call or clinic visit) and subsequent anticancer therapy approximately every 3 months after EoS Visit until death, loss to follow-up, or study termination by Roche, whichever occurs first

End of Study

After the completion of induction therapy patients will continue maintenance therapy for a maximum of 24 months unless the occurrence of disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision. All patients, also in case of early discontinuation, will attend a safety visit (5 ± 1 weeks) after receiving the last administration of RO5520985, which is the End of Study (EoS) Visit. Patients off study will receive standard of care for the stage of their disease.

Follow-up for survival will continue until all patients have either died or are lost to follow up, or the sponsor decides to end the trial, whichever occurs first.

The study will formally end once the survival follow-up is complete or the last patient has completed the EoS Visit or is withdrawn from the study prior to that time (whichever occurs last), but may be prematurely terminated by the Sponsor. The main analysis and reporting will be conducted once approximatelly 80 PFS events have been collected, When the study is formally ended, an additional analysis will be performed and appended to the main report.

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) graded according to the National Cancer Institute Common Terminology Criteria

for Adverse Events (NCI CTCAE) v4.03

- Changes in hematology, biochemistry, coagulation, specifically those associated with vascular and renal function
- Physical examinations (including ECOG), vital signs and ECG
- Incidence and titers of human anti-human antibodies (HAHAs)
- Adverse events leading to RO5520985, bevacizumab, or chemotherapy discontinuation
- Incidence of the following selected adverse events according to NCI CTCAE, v4.03:

  Arterial hypertension (Grade ≥ 3)

  Proteinuria (Grade ≥ 3)

  Arterial thromboembolic events (any grade)

  Venous thromboembolic events (Grade ≥ 3)

  Vascular disorder - other: Thrombotic microangiopathy (any grade)

  Gastrointestinal perforation (any grade)

  Fistula involving an internal organ (any grade)

  Fistulae (Grade 4)

  Wound dehiscence/complication (Grade ≥ 3)

  Bleeding/hemorrhage (Grade ≥ 3)

  Pulmonary bleeding (Grade ≥ 2)

  CNS bleeding (Grade ≥ 2)

  Congestive heart failure (Grade ≥ 3)

  Reversible posterior leukoencephalopathy syndrome (any grade)

PHARMACOKINETIC OUTCOME MEASURES

The pharmacokinetic (PK) outcome measures for this study are as follows:

- The PK profile of RO5520985 will be characterized with the plasma concentration-time data following IV administration of RO5520985, and will include the following parameters: C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC, AUC_{τ}, CL, V_{ss}, accumulation ratio (RA)
- The PK profiles of oxaliplatin (free and total) and 5-FU will be characterized with the plasma concentration-time data following IV administration of FOLFOX, and will include the following parameters: C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC (when applicable)
- Additional PK parameters may be evaluated as appropriate

EFFICACY OUTCOME MEASURES

Primary Outcome Measure

The primary outcome measure for Study BP29262 is progression-free survival (PFS), defined as the time from randomization to the date of first documented occurrence of progression based on RECIST v1.1 criteria as determined by the Investigator or death from any cause on study, whichever occurs first.

Secondary Outcome Measures

The secondary outcome measures for Study BP29262 are as follows:

- Objective response rate (ORR). Objective response rate is defined as the rate of patients with an objective tumor response, i.e. partial response (PR) or complete response (CR) as determined by the Investigator using RECIST v1.1 criteria on two consecutive occasions at least 4 weeks apart
- Duration of response, defined as the first occurrence of a documented objective response until the time of progression or death from any cause on study
- Overall Survival, defined as the time from randomization until death from any cause

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study include but are not limited to the following:

- Levels of circulating targets by comparing baseline versus on-treatment values of Ang-2 and VEGF-A and their differential expression/regulation during RO5520985 vs. bevacizumab therapy
- Changes of PlGF from baseline during treatment as marker of unspecific endothelial stress response and as potential response towards RO5520985
- Assessment of tissue and soluble blood markers potentially related to predicting clinical benefit or toxicity of RO5520985 vs. bevacizumab
- An assessment of tumor growth kinetics will be made by comparing post-treatment scans with at least 2 pretreatment scans not older than 12 weeks prior to C1D1, if available.
- Analysis of additional CT parameters including necrotic volume/total tumor volume and intensity to assess their potential value as early response prediction markers

BIOMARKER/GENOTYPING SAMPLE COLLECTION

Pharmacodynamics and Exploratory Biomarker Assessments

The following samples will be collected for exploratory analyses:

- Plasma
- Archival primary tumor tissue

Please note: Soluble biomarkers (plasma) will be assessed in Part II patients only.

Plasma

Approximately 7.5 mL blood sample, for plasma isolation will be obtained for each timepoint. The plasma will be used for the following assessments:

- Levels of circulating targets: Ang-2 and VEGF-A
- Angiogenesis-related markers (but not limited to): Ang1, PlGF, sTie-2, VEGF-C, sVEGF-R1, sVEGF-R2, sVEGF-R3, SDF-1α, E-selectin, ICAM-1, bFGF, IL-8, PDGF-C, CA-IX

Blood (2mL) for plasma isolation will be obtained at baseline, disease progression as well as end of study and

be used to measure levels of circulating MMP-2 and MMP-9.

An additional approximate 2 mL blood sample will be collected at baseline for potential development of an Ang-2 companion diagnostic test, as well as a total of approximately 6 mL blood for 3 additional measurements of Ang-2.

In addition 10 mL blood sample for plasma isolation will be required for the following assessment:

- Dependent on the mutational analysis of the archival tissue based on the specific mutation detected, the presence of circulating tumor DNA (ctDNA) will be assessed at baseline and various time points on treatment

Total blood loss

The total blood volume loss for plasma and whole blood biomarker assessments will be approximately 140 mL up to Cycle 13 including the Disease Progression and End of Study Visit.

Archival Primary Tumor Tissue

Representative tumor specimens in formalin-fixed, paraffin embedded blocks (preferred) or slides (35 slides if possible) with an associated pathology report are to be obtained for all patients from all sites. Tumor blocks/slides must be sent for central extended analysis of the RAS mutational status.

In addition tumor tissue will be analyzed to assess further potential response prediction markers. This includes the analysis of (but is not limited to):

- Target proteins and biomarkers related to their vascular signaling including Ang-2, VEGF-A, Ang-1, Tie-2
- Markers of vessel architecture by IHC including CD31, CD34, Podoplanin, aSMA, c-C3, Ki67. The analysis will be prioritized based on the amount of material available. Additional assessments may be performed.
- Markers characterizing the tumor status including Ki67 and CAIX. The analysis will be prioritized based on the amount of material available. Additional assessments may be performed.
- Markers of tumor-infiltrating immune cells including CD4, CD8, CD3/FOXP3, CD68/CD163, CD3/perforin. The analysis will be prioritized based on material and assay availability. Additional assesments may be performed.
- Molecular mutational analysis including, but not limited to mutational status of EGFR, BRAF, etc.

INVESTIGATIONAL MEDICINAL PRODUCTS

RO5520985

RO5520985 will be administered once every two weeks (Q2W) at a fixed dose of 2000 mg IV on Day 1 of each Cycle prior to mFOLFOX-6.

Bevacizumab

Bevacizumab will be administered at a dose of 5 mg/kg IV on Day 1 of each Cycle prior to mFOLFOX-6. Bevacizumab will be dosed by body weight. The weight at screening will be

used for dose calculation for each patient. Recalculation of dosage is not required if weight changes.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Modified FOLFOX-6 (5-FU, folinic acid and oxaliplatin)

- Oxaliplatin at a dose of 85 mg/m^2 IV over 120 ($\pm$5) minutes on Day 1 of each Cycle.
- Folinic acid at a dose of 400 mg/m^2, IV over 120 ($\pm$15) minutes on Day 1 of each Cycle. As an alternative, Levofolinic acid at a dose of 200 mg/m^2, IV over 120 ($\pm$15) minutes on Day 1 of each Cycle can be given.
- 5-fluorouracil (5-FU) starting bolus on Day 1 of each Cycle at a dose of 400 mg/m^2 followed by 2400 mg/m^2 IV permanent infusion for 46 ($\pm$2) hrs.

The preferred order and rate of drug administration may be modified based on patient tolerability or institutional guidelines. In the event that the full dose of folinic acid (racemic leucovorin or levoleucovorin) is unavailable and in accordance with NCCN guidelines, the dose may be lowered in accordance with the treating physician's standard practice in administering mFOLFOX-6. In case neither racemic leucovorin nor levoleucovorin is available, dose may be omitted and patients who tolerate treatment without Grade 2 or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered. However, standard dosing should be resumed when supply is adequate.

During induction phase substitution of 5-FU/folinic acid is not permitted. During the maintenance phase substitution of 5-FU/folinic acid IV by oral capecitabine is discouraged. However, individual patients may receive capecitabine without folinic acid according to institutional standards (e.g., 625 mg/m^2 BID continuously during maintenance phase at the discretion of the Investigator and in agreement with the Sponsor's medical monitor.

PROCEDURES:

Physical Examinations

Physical examinations will occur throughout the study according to the Schedule of Assessments (SoA). A complete physical examination should include an evaluation of the head, eyes, ears, nose and throat. The cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurological systems should also be examined. Any abnormality identified at baseline should be recorded on the Medical History eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

ECOG Performance Status

Performance Status (PS) will be measured using the ECOG Performance Status Scale. PS will be assessed with each physical exam. It is recommended, where possible, that a patient's PS will be assessed by the same person throughout the study.

Vital Signs

Vital signs will include measurements of blood pressure, respiratory rate, body temperature and pulse rate (in sitting position upon resting for 5 minutes). Medically significant findings that are present prior to the start of study treatment must be recorded in the Medical History

eCRF with “ongoing” ticked. Medically significant findings made after start of study treatment or worsening of those reported at baseline and which meet the definition of an AE must be recorded as an AE in the eCRF.

Electrocardiograms

A 12-lead ECG will be performed and should be obtained for each patient from the same machine, whenever possible, as indicated in the SoA or as clinically indicated. Triplicate ECG recordings will be obtained within approximately 2–5 minutes of each other. The average of the three readings will be used to determine ECG intervals (e.g., PR, QT).

Transthoracic Echocardiogram/Multiple Gated Acquisition Scans

TTE (transthoracic echocardiogram) or MUGA (multiple gated acquisition) scan will be performed according to the standard practice of the investigational site. This may be further repeated at the Investigator’s discretion if there are signs or symptoms of cardiotoxicity. TTE or MUGA scan will be used to monitor the cardiac parameters of function (i.e., left ventricular ejection fraction [LVEF]).

Adverse events

Adverse events will be graded according to the NCI Common Terminology Criteria (NCI–CTCAE) version 4.03.

Safety Laboratory Assessments

The following safety laboratory assessments will be performed according to the SoA:

- Hematology: Hemoglobin, hematocrit, platelet count, RBC count (erythrocytes), WBC count (leukocytes), WBC absolute differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes).
- Serum chemistry: Na, K, Ca, lipase, glucose, GGT, AST, ALT, LDH, AP, total and direct bilirubin, urea, creatinine, total protein, albumin, CK, TSH, CRP and CrCl calculated (by Cockroft-Gault formula) or directly measured.
- Coagulation: INR/PT; aPTT, fibrinogen.
- Blood tumor marker: CEA
- Urine analysis: Urine dipstick for proteinuria (24-hrs urine protein analysis in 2+ or greater urine dipstick reading).
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum or urine pregnancy test at Screening. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

All samples for safety laboratory assessments will be sent to the study site's local laboratory for analysis. Normal ranges for the study laboratory parameters must be supplied to the CRO before the study starts. The total amount of blood drawn for all above described safety parameters will be approximately 12 mL during screening and approximately 12 mL for each subsequent safety laboratory assessment.

Pharmacokinetic Assessments

Part I of the study

PK samples for RO5520985 and FOLFOX will be collected as outlined in the SoA. For each scheduled time point of RO5520985 and 5-FU, an approximate venous blood volume of 2 mL for each compound will be drawn. For each scheduled time point of oxaliplatin (free and total), an approximate venous blood volume of 4 mL will be drawn..

In Part I, the total amount of blood drawn for PK (including HAHA) is approximately 149 mL.

Part II of the study

Samples for RO5520985 PK analysis will be collected as outlined in the SoA. Samples from patients receiving bevacizumab will be taken as per the RO5520985 schedule to maintain the double-blind design of the study, but will not be analyzed. PK parameters of FOLFOX will not be measured in Part II of the study. At each scheduled timepoint approximately 2 mL of venous blood will be drawn.

In Part II, the total amount of blood drawn for PK (including HAHA) is approximately 70 mL.

Human Anti-Human Antibodies

Sampling will be conducted to determine if HAHAs are developed against RO5520985. Samples from patients receiving bevacizumab will be taken as per the RO5520985 schedule to maintain the double-blind in the study, but will not be analyzed. For analysis purposes approximately 2 mL of venous blood for plasma isolation will be drawn.

Disease-Specific Assessments

Tumor and Response Evaluations

Throughout the trial, the RECIST criteria, v. 1.1 will be applied when assessing any responses to the study drug treatment. All potential sites of tumor lesions will be assessed at baseline by radiologic techniques using contrast enhanced CT or MRI imaging. All tumor lesions at baseline need to be recorded as either target or nontarget lesions.

The minimum schedule of imaging is the thorax, abdomen and pelvis. If there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule, further investigations should be performed with a view to documenting the full extent of the tumor burden at baseline according to the Investigator's clinical judgment (and according to RECIST). Patients with target lesions that have become centrally necrotic and meet the RECIST criteria of progressive disease, but otherwise demonstrate clinical symptoms improvement and tumor marker decrement, may remain on study treatment upon decision of the Investigator and the Sponsor's medical monitor.

STATISTICAL METHODS:

Safety

The safety analysis population will include all patients (Part I and Part II) who receive any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985). Patients will be assigned to the treatment arm received.

Safety analyses include:

- Adverse events
- Clinical Laboratory Test Results
- Vital Signs
- ECG Data Analysis
- Concomitant Medications

Pharmacokinetics

PK analyses will include all patients who received any amount of study treatment (5 FU/folinic acid, oxaliplatin, bevacizumab, or RO5520985), the same as the safety analysis population.

Patients may be excluded from the PK analysis population if they significantly violate the eligibility criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the pharmacokinetic analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

All pharmacokinetic parameters will be presented by listings and descriptive summary statistics separately by group or cohorts.

Additional PK analyses will be conducted as appropriate.

Efficacy

Primary and secondary efficacy analyses will be based on the intent to treat (ITT) population. It will include all patients who were randomized (Part II only) and received any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985). Patients will be assigned to the treatment arm to which they were randomized.

Efficacy analyses include the following.

Primary Efficacy Endpoint

- Progression-free survival (PFS) defined as the time between

randomization and the date of first documented disease progression or death from any cause on study, whichever occurs first. Progression will be based on tumor assessment made by the Investigator according to RECIST 1.1 criteria.

Secondary Efficacy Endpoints

- Objective Response Rate (ORR) determined as the rate of patients with an objective tumor response (complete [CR] or partial response [PR]). Objective response (OR) is defined as a complete or partial response as determined by the Investigator using RECIST v1.1 on two consecutive occasions at least 4 weeks apart.
- Duration of OR defined as the time from the initial response (CR or PR) to disease progression or death from any cause on study. This will only be calculated for patients who have a best overall response of CR or PR.
- Overall Survival (OS). OS is defined as the time from randomization until death from any cause. All deaths will be included, without regard to whether they occur on study or following treatment discontinuation. For patients who have not died, OS will be censored at the last date known to be alive. Patients without any post baseline information will be censored at the time of randomization.

Exploratory Biomarker Analyses

Exploratory biomarker parameters may be presented by listings and descriptive summary statistics separately by treatment arms.

All analyses of PD and exploratory biomarkers will be based on the safety analysis population of Part II patients, i.e. any Part II patients who received any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985).

To assess predictability of a biomarker, the association between clinical outcome and the biomarker level or changes thereof will be explored. Details of the biomarker analysis are provided within the Statistical Analysis Plan (SAP).

Other Exploratory Analyses

PK/PD

Exploratory graphical analyses of exposure-efficacy relationships may be produced for selected efficacy, PD and/or safety measurements if feasible. A PK/PD modeling approach may be considered in order to further explore the exposure-response relationship of selected response variables.

Tumor growth kinetic

An exploratory assessment of tumor growth kinetics will be made by comparing post-treatment scans with at least 2 pre-treatment scans not older than 12 weeks prior to C1D1, if available. The two pre-treatment scans consists of a pre-study scan (if available) and the study baseline scan, and will allow estimation of tumor growth rate before start of treatment. If the pre-treatment tumor growth kinetic can be assessed, this will then be compared to the growth/shrinkage rate after start of treatment. Data will be explored using linear and/or exponential models, as appropriate, in non linear mixed effect modelling software.

SAMPLE SIZE JUSTIFICATION:

Within Part I, 6-18 patients will be treated with RO5520985 plus mFOLFOX-6. Six patients per RO5520985 dose to be tested is considered sufficient to assess the safety and tolerability of RO5520985 in combination with mFOLFOX-6.

Part II of the study will enroll approximately 190 patients, and the primary analysis will be

performed after approximately 80 investigator assessed PFS events. The emphasis of the efficacy analysis will be on estimation of the magnitude of treatment effect rather than hypothesis testing. This trial is hypothesis-generating and is designed to be able to detect a meaningful benefit of the combination therapy of RO5520985 plus mFOLFOX-6 versus bevacizumab plus mFOLFOX-6. Based on the sample size of 80 events observed in the two treatment arms combined, there is an 80% power to detect a HR of 0.574 at a one-sided significance level of 0.05.

Interim Analyses

Interim safety analysis of Part I patients will be performed by an internal monitoring committee (IMC) after all patients have received at least two full cycles. The IMC may also conduct further blinded safety reviews based on safety signals that arise at any time during Part II of the study.

Within Part II of the study, an interim analysis for futility is planned to be conducted after approximately 30 PFS events. A cut-off HR of 1.0 has been suggested as non binding futility criteria. The probability of observing an HR equal or higher than 0.77 at final analysis, given an HR of 1.0 at the interim analysis, will be above 80%. Enrollment will not be stopped during the interim analysis.

Administrative interim analysis, based on efficacy, may also be performed during Part II of the study after approximately 30 events and again after 50 events. The efficacy interim analyses are administrative in nature allowing for decision making of subsequent clinical development activities (i.e., pivotal Phase III study) of the compound under investigation. The study will not be stopped for efficacy. Separate from the Safety IMC, there will be in addition an Efficacy IMC responsible for the futility/efficacy analysis of Part II. The details and modalities are described in a pre-specified charter outlined in a separate document as well as in the statistical analysis plan.

List of Prohibited Medications

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and Clinical Pharmacologist/Clinical Scientist.

The following treatments are not permitted during the study:

- Any other investigational therapy
- Anticancer therapy (chemotherapy, hormonal, biological or radiation therapy, and surgery) other than study treatments
- Radiotherapy, except short course palliation

If any of these therapies are needed, the patient will be considered to have evidence of progressive neoplastic disease and have experienced treatment failure. This will lead to the patient's discontinuation from the study.

Furthermore, due to the potential risk of bleeding associated with anti-angiogenic therapies, the following treatments are prohibited:

- Current use of full dose anticoagulants or thrombolytic therapy at therapeutic doses. **However, if a patient experiences a VTE event while still receiving study drug treatment, it may still be possible for him or her to remain on study medication. Please see Section 5.2.3.2 (Table 2) for guidance on further treatment with or discontinuation of bevacizumab/ RO5520985 therapy.**
- Prophylactic use of low dose anticoagulation, unfractionated heparin or low molecular weight heparin (LMWH) is permitted. However, the preferred choice for anticoagulation treatment should be LMWH as per ASCO guidelines. The prophylactic use of warfarin or coumarin-like products is not permitted.
- Prophylactic use of anticoagulation at baseline and during study treatment for the maintenance of patency of permanent indwelling central venous access devices is permitted. If a patient suffers a VTE event, while still receiving study treatment, it may still be possible for him or her to remain on study treatment (Section 5.2.3)

In addition, due to the potential risk of severe/fatal infections in patients treated with 5-FU, the following treatment is prohibited:

- Vaccination with live vaccines

Also prophylactic use of phenytoin is not allowed in combination with 5-FU.

Concomitant **chronic** use of NSAIDs while receiving study drugs is **prohibited. However, for the symptomatic relief of medical conditions (e.g. headache, fever) sporadic or short-term intake of oral NSAIDs is allowed, when co-administered proton pump inhibitors to reduce potential gastrointestinal damage. Also** seek consultation with a gastroenterologist as medically indicated.

Chronic daily treatment with systemic corticosteroids (dose >10 mg/day methylprednisolone equivalent) is generally prohibited while on RO5520985/ bevacizumab. However, a one-time or medically indicated, short course of higher dose (>10 mg/day methylprednisolone equivalent) of systemic corticosteroid use may be allowed as agreed by the study investigator and the Medical Monitor.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse events
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AUC	area under the curve
BID	twice daily
C	Cycle
CL	Clearance
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
D	Day
DP Visit	Disease Progression visit
EC	ethics committee
ECG	Electrocardiograms
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EIH	entry into human
EoS	end of study
ESF	Eligibility Screening Form
ESMO	European Society of Medical Oncology
EU	European Union
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FOLFIRI	irinotecan, folinic acid, and 5-fluorouracil
FOLFOX	oxaliplatin, folinic acid, and 5-fluorouracil
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
G	grade
GIP	**Gastrointestinal perforation**
HAHA	human anti-human antibody

HIV	human immunodeficiency virus
HR	hazard ratio
HUVEC	human umbilical vein endothelial cell
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFL	irinotecan, 5-fluorouracil, and leucovorin
IMC	internal monitoring committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	institutional review board
IRR	infusion-related reactions
IV	intravenous
IxRS	interactive (voice/web) response system
LMWH	low molecular weight heparin
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
mCRC	metastatic colorectal cancer
MRI	magnetic resonance imaging
MSI	microsatellite instability
MVD	microvessel density
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
OR	objective response
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PlGF	placental growth factor
PR	partial response
PRIND	prolonged reversible ischemic neurologic deficit
PS	performance status
RCR	Roche Clinical Repository
RCT	randomized controlled trials
RECIST	Response Evaluation Criteria in Solid Tumors
RoW	Rest of World
RP2D	recommended Phase II dose

PRIND	Prolonged Reversible Ischemic Neurologic Deficit
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoA	Schedule of Assessments
SoC	Standard of Care
SPA	statistical programming analyst
TGI	tumor growth inhibition
TIA	Transient ischemic attack
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
XELOX	oxaliplatin and capecitabine

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Colorectal cancer (CRC), a cancer with origins within the colon or the rectum, is the second leading cause of cancer deaths in the Western world in males and females (Arnold and Seufferlein 2010). In 2013, the number of new cases of colon cancer and rectal cancer were estimated to be approximately 102,480 and approximately 40,340 respectively; with an estimated 50,830 people who died from the disease (colon and rectal cancer combined) (National Cancer Institute).

The major cause of death in patients with CRC is distant metastasis (Alberts and Wagman 2008). Depending on the stage of the primary tumor, liver metastases are seen in 20–70% of patients with CRC, and lung metastases are seen in 10–20% (Penna and Nordlinger 2002); with the liver being the only site of metastatic spread in 30-40% of patients (Garden et al. 2006). Without treatment, the median survival for patients with metastatic CRC is approximately 1 year (Liu et al. 2003). Surgical resection of metastases can improve this result dramatically, with 5-year survival rates approaching 27–41% in appropriate patients (Mandala et al. 2007). However, only 10–20% of patients with metastatic disease have lesions that are considered resectable at presentation (Vilbert et al. 2005).

The optimal treatment strategy for patients with clearly unresectable metastatic CRC (mCRC) is rapidly evolving. Chemotherapy plays a central role in treatment regimens for mCRC and is recommended for use as a treatment in patients with unresectable disease or as a neoadjuvant/adjuvant treatment in patients with resectable disease (Van Cutsem et al. 2010; Benson et al. 2013). Typical chemotherapy regimens for mCRC include: Oxaliplatin, folinic acid, and 5-fluorouracil (FOLFOX) or irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) ± bevacizumab, or FOLFOX or FOLFIRI ± cetuximab or panitumumab.

1.2 ANTI-ANGIOGENIC TREATMENT OF COLORECTAL CANCER

The process of new blood vessel formation, or angiogenesis, has become an important therapeutic target in many different cancers including mCRC. To grow beyond 1–2 mm in diameter, a tumor needs an independent blood supply, which is acquired by the overexpression of growth factors that recruit new vasculature from existing blood vessels. Disruption of the delicate balance of pro- and anti-angiogenic factors, described as the angiogenic switch, results in the creation and maintenance of a growing vascular network (Bergers and Benjamin 2003; Ferrara 2004; Hicklin and Ellis 2005). It has been hypothesized that inhibition of angiogenesis in tumors can both impair the formation of new tumor blood vessels and possibly ‘normalize’ the existing tumor vasculature, causing a more efficient delivery of cytotoxic chemotherapies (Grothey and Allegra 2012). At present, a number of anti-angiogenic agents are in clinical development or have been approved for the treatment of patients with mCRC.

1.2.1 Anti-VEGF mAb Treatment of Colorectal Cancer

The development and use of antiangiogenesis agents, particularly those targeting vascular endothelial growth factor (VEGF), has become an integral component of anticancer chemotherapy regimens for many tumor types including CRC (Meadows et al. 2012; Wang and Lockhart 2012). Bevacizumab, an anti-VEGF antibody, should be considered in patients with metastatic CRC, as it increases the activity of an active cytotoxic regimen (Van Cutsem et al. 2010). In a large Phase III trial (AVF2107g) with patients who have mCRC, the addition of bevacizumab to the "IFL" regimen (irinotecan plus bolus 5-fluorouracil [5-FU]/leucovorin chemotherapy resulted in a clinically and statistically significant increase in overall survival (OS), with a hazard ratio (HR) for death of 0.66 (median OS: 20.3 vs. 15.6 months, $p < 0.001$). Similar increases were seen in progression-free survival (PFS) (10.6 vs. 6.2 months, $p < 0.001$ HR = 0.54), objective response rate (ORR) (44.8% vs. 34.8%), and duration of objective response (OR) (10.4 vs. 7.1 months; $p < 0.001$) for the combination arm versus the chemotherapy alone arm (Hurwitz et al. 2004). On the basis of the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved by the FDA in 2004 and by the EMA in 2005 for for use in combination with infusional 5-FU–based chemotherapy as first-line treatment for patients with mCRC. In subsequent studies bevacizumab demonstrated improved clinical outcomes in combination with nearly all chemotherapy regimens, including intravenous (IV) 5-FU/leucovorin (Kabbinavar et al. 2005), oral 5-FU (capecitabine) (Tebbutt et al. 2010), and IV or oral 5-FU combined with oxaliplatin (FOLFOX or XELOX regimens) (Giantonio et al. 2007; Saltz et al. 2008). Improvements were also suggested when bevacizumab was combined with infusional 5-FU and irinotecan (FOLFIRI regimen) (Fuchs et al. 2007). Additional data from a Phase III trial in second-line mCRC (E3200) has also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX second-line chemotherapy resulted in improved OS compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, $p < 0.01$ HR = 0.75) in a population of CRC patients who were previously treated with a chemotherapy regimen (Giantonio et al. 2007).

1.2.2 Anti-Angiopoietin-2 Treatment of Colorectal Cancer

The VEGF pathway and the angiopoietin-Tie2 receptor axis have distinct roles in the regulation of pathologic angiogenesis (Huang et al. 2010). Angiopoietin-2 (Ang-2) is an inhibitory ligand of the Tie-2 receptor that is stored in the Weibel–Palade bodies of endothelial cells (Fiedler et al. 2004) and disrupts the integrity of the blood vessel wall, thus counteracting vascular normalization (Maisonpierre et al. 1997; Scharpfenecker et al. 2005; Falcon et al. 2009). Ang-2 is overexpressed and appears to be a prognostic factor in a number of tumor types, including CRC (Bach et al. 2007). High serum Ang-2 levels have been shown to promote metastatic growth (Imanishi et al. 2007) and are associated with poorer survival outcomes in colon cancer (Volkova et al. 2011). Furthermore, higher tumor Ang-2 expression has been associated with lymph node metastasis, venous invasion, and high microvascular density in CRC

(Chung et al. 2006). Ang-2 biology is known to be VEGF–dependent and has been shown to be downregulated in response to anti-VEGF therapy (Liu et al. 2013). In fact, amongst patients receiving bevacizumab-containing treatment, low Ang-2 baseline levels correlated with longer PFS and OS and greater reductions in Ang-2 level also predicted for better OS (Goede et al. 2010; Liu et al. 2013). The consistency of these pre- and on-treatment results not only suggests that Ang-2 may be a predictor of benefit from anti–VEGF-containing therapy but also underscore the potential value of concurrently targeting VEGF and Ang-2/Tie2. Recently, different approaches have been described to target the Angiopoietin/Tie axis including Tie2 kinase inhibitors, Fc-fusion proteins and monoclonal antibodies with different specificities, and new scaffolds like CovX which are presently in pre-clinical or clinical exploration (Brown et al. 2010; Huang et al. 2011; Cascone and Heymach 2012). Trebananib (AMG 386) is an investigational, intravenously administered peptide-Fc fusion protein neutralizing the interaction between Ang-1 or Ang-2 and the Tie2 receptor that was recently tested as second-line treatment for patients who have mCRC (Peeters et al. 2013). In this Phase II study, the combination of trebananib plus FOLFIRI had acceptable toxicity but did not prolong PFS compared with placebo plus FOLFIRI, although there was a trend towards improved ORR. The authors concluded that treatment approaches incorporating inhibitors of the Ang/Tie2 axis could have potential in the treatment of CRC if administered at the right dose/schedule, in less advanced disease and administered in combination with VEGF inhibitors. Trebananib plus bevacizumab in patients with chemotherapy-naïve metastatic CRC is under clinical evaluation in a Phase II study (ClinicalTrials.gov, NCT01249521).

1.3 BACKGROUND ON RO5520985

RO5520985 is based on bevacizumab, a monoclonal antibody targeted against VEGF-A, as well as a monoclonal antibody targeted against Ang-2 called LC06. It is a bispecific monoclonal antibody based on a human IgG1 framework and is comprised of two different heavy chains and two different light chains. One arm of the antibody binds Angiopoietin-2 (Ang-2) and the other arm binds Vascular Endothelial Growth Factor A (VEGF-A). Point mutations in the CH3 domain (“Knobs-into-holes”) promote the assembly of two different heavy chains. Exchange of the constant part of the heavy chain 1 and constant part of the light chain domains in the Ang-2 binding Fab promote the correct assembly of the two different light chains called the “CrossMab approach” (Schaefer et al. 2011).

Ang-2 and VEGF-A cooperatively promote tumor growth in mouse tumor models, as demonstrated by the inability of Ang-2 overexpression to stimulate the growth of hepatocellular carcinoma unless VEGF-A is simultaneously upregulated (Yoshiji et al. 2005). Thus, selectively targeting both Ang-2 and VEGF-A might increase the level of normalization that is achieved by reducing the proportion of unstable blood vessels that initiate angiogenesis in cancer patients. In syngeneic and xenograft mouse tumor models, the physical combination of anti-Ang-2 with anti-VEGF-R2 inhibitor or

anti-VEGF-A antibody led to enhanced anti-tumor activity relative to the use of the single agents, supporting the concept that concurrent pathway inhibition may also improve anti-angiogenic cancer therapies in the clinic (Hashizume et al. 2010; Brown et al. 2010).

Further information can be obtained from the RO5520985 Investigator's Brochure (IB).

1.3.1 Previous Nonclinical Studies

RO5520985 was shown to bind selectively and with high affinity both VEGF-A and Ang-2 in a concentration dependent manner. The VEGF-A binding arm is crossreactive to VEGF-A in rabbit, cynomolgus monkey, and human but not mouse. The Ang-2 binding arm is cross-reactive to rabbit, cynomolgus monkey, human, and mouse Ang-2.

In vitro binding of RO5520985 to Ang-2 inhibited (1) binding of the Ang-2 ligand to Tie2 receptor, and (2) Ang-2–mediated Tie2 phosphorylation. In vitro binding of RO5520985 to VEGF inhibited (1) VEGF-A–induced proliferation of HUVEC (human umbilical vein endothelial cell) proliferation, and (2) VEGF-A–induced HUVEC migration.

The anti-angiogenic effect of RO5520985 was investigated in the VEGF-A–induced mouse cornea pocket assay. Systemic administration of either RO5520985 or bevacizumab completely abolished VEGF–induced corneal angiogenesis. Single agent treatment with LC06 (Ang-2 inhibitor) exerted a less pronounced effect.

Tumor growth inhibition (TGI) and improved survival following treatment with RO5520985 was demonstrated in vivo in multiple cell lines, patient-derived xenografts, and syngeneic mouse models (including gastric, colorectal, lung, breast, ovarian, glioma, lymphoma, prostate and pancreatic tumors). The pharmacokinetics of RO5520985 were determined in mice and yielded a typical IgG-like terminal half-life in the range of 6–7 days. On the basis of the findings of a dose dependency study in the CRC xenograft model Colo205, a dose of 10 mg/kg was considered optimal for use in subsequent studies.

In another Colo205 xenograft study, tumor growth was significantly inhibited by single-agent bevacizumab (TGI of 66%) and single-agent LC06 (TGI of 47%), whereas the bispecific RO5520985 administered at an equivalent dose in terms of binding sites induced tumor stasis and exhibited a TGI of 92% at the end of the study. Additionally, tumor cell dissemination to the lung was reduced by RO5520985 in the same study. RO5520985 also showed superior anti-tumor activity compared to the monotherapies in small versus large Colo205 and KPL-4 tumors making it an attractive drug because vessel structure changes in growing tumors from immature to mature vessels.

Anti-tumor activity of RO5520985 was also observed in ovarian, pancreatic, prostate and lymphoma xenografts. Combination of anti-VEGF-A and anti-Ang-2 also showed strong anti-tumor activity when tested in two syngeneic mouse models (colon and breast) as indicated by over 60% TGI.

Vessel architecture was analyzed in several mouse models. Microvessel density (MVD) was significantly reduced in orthotopic KPL-4 breast cancer xenograft. Remaining vessels were highly covered with pericytes indicating vessel normalization induced by RO5520985. Similar effects were observed in an orthotopic glioblastoma model (U87): as compared to anti-Ang-2 or anti-VEGF-A treatment, the combination of anti-Ang-2 and anti-VEGF-A antibodies resulted in superior anti-tumor activity which translated into prolonged survival. MVD and vessel volume were significantly decreased in the anti-Ang-2/anti-VEGF-A combination group compared to monotherapy. Vessel architecture and function changed towards a more normal vessel phenotype, indicating vessel normalization induced by anti-Ang-2/VEGF-A treatment. This was demonstrated by reduced vessel turnover and increased blood cell velocity. Similar findings regarding TGI were observed in a subcutaneous U87 cancer xenograft.

Further details on nonclinical studies can be found in the RO5520985 IB.

1.3.2 Previous Clinical Studies

Initial clinical experience with RO5520985 is based on the ongoing entry into human, Phase I study (Study BP28179; NCT01688206). This is an open-label, multicenter, Phase I dose-escalation study in patients with solid tumors to assess the safety, tolerability, PK, PD and preliminary anti-tumor activity of RO5520985. The study consists of three parts: Part I, a dose escalation phase to evaluate the maximum tolerated dose (MTD) and/or recommended as Phase 2 dose (RP2D) followed by Part II and Part III, which start in parallel. Part II is designed to assess the pharmacodynamic (PD) effects of RO5520985 in paired tumor biopsies and by tumor imaging and Part III to investigate the single agent activity of RO5520985 in patients with platinum resistant/refractory ovarian cancer.

As of the cutoff date (8 January 2014), a total of 42 patients have been treated within Part I of the study with intravenous RO5520985 at the dose levels presented in Table 1 .

Table 1 Cohorts and Dosing Regimen for Part I (Dose Escalation)

	Dose Escalation Cohorts							Extension Cohorts	
Cohort	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Dose (mg/kg)	3	6	12	19.2	10	20	30	30	30
Regimen	Q2W	Q2W	Q2W	Q2W	QW	QW	QW	Q2W	QW
Number of patients	1	3	4	8	4	4	6	6	6

The dose-escalation part of the study is completed and the MTD has not been reached. Part II and Part III of the study commenced in February 2014.

Clinical Pharmacokinetics

Blood samples sufficient for the estimation of PK parameters of RO5520985 have been analyzed for all 42 patients treated with RO5520985 in Part I of Study BP28179 using both a bi-weekly (Q2W) and weekly (QW) dosing regimen.

RO5520985 was infused over a 90-minute period for the first dose. The infusion period was reduced to 60 minutes for the second dose and to 30 minutes for all subsequent doses. The PK profile to date shows a near linear increase in exposure (AUC) and peak concentrations (C_{max}) across the dose-range studied, with low inter-individual variability (3–36%) for both Q2W and QW regimens. The elimination half life following a Q2W regimen is 7–9 days.

Safety

Within Study BP28179, all patients (42/42, 100.0%) from all cohorts experienced at least one adverse event (AE), regardless of causality. Among the 42 patients, 328 AEs were recorded (174 AEs in Q2W, 154 AEs in QW). The most commonly reported AEs were hypertension (50.0%), asthenia (35.7%), headache (28.6%) and fatigue (19.0%). The majority of the AEs were of Grade 1 or Grade 2 intensity. Overall, 20 patients experienced 33 Grade $\geq$ 3 AEs; 12 patients in the Q2W schedule experienced 21 Grade $\geq$ 3 AEs and 8 patients in the QW schedule had 12 Grade $\geq$ 3 AEs. Sixteen of these AEs were considered by the Investigator to be related to RO5520985 (10 in QW and 6 in Q2W). Overall, the most frequently reported individual Grade $\geq$ 3 AE was hypertension (19%, 8/42 pts) which was reported in 2 patients in the Q2W schedule and 6 patients in the QW schedule. All of these Grade 3 hypertension events were considered by the investigator to be related to study treatment.

Nine SAEs have been reported, 5 of which were judged by the Investigator to be related to RO5520985 (Grade 5 pulmonary hemorrhage at 19.2 mg/kg Q2W, Grade 3 vesico-cutaneous fistula at 12 mg/kg Q2W and in the 30 mg weekly cohort Grade 2 cerebral hemorrhage, Grade 3 hypertension and Grade 3 thrombotic microangiopathy. All related SAEs led to discontinuation of study treatment.

The fatal pulmonary hemorrhage occurred in a CRC patient receiving 19.2 mg/kg Q2W that constituted a DLT; however, this SAE was also reported and judged by the Investigator to be possibly related the patient's underlying tumor disease with a large centrally located mediastinal metastasis. The patient had pre-existing episodes of hemoptysis G1 and cough G1 at study entry.

Anti-tumor activity

As of the cutoff date (8 January 2014), 32 out of 42 patients were available for evaluation of the best overall response according to RECIST criteria. Among the 32 patients, 1 patient in the QW schedule (30 mg/kg) had a partial response. Sixteen patients had stable disease (11/22 patients in Q2W, 5/20 patients in QW) and 15 patients had progressive disease (7/22 patients in Q2W, 8/20 patients in QW) as best

response. A total of 8 patients could not yet be assessed for response and for 2 patients no assessment is available. Eligible patients underwent DCE-MRI demonstrating moderate to significant on-treatment reductions in parameters representative of vascular characteristics in 22/34 (64%) patients evaluated. DW-MRI showed hints of on-treatment reduction in cell density and increase in necrosis in 7/25 (28%) patients evaluated.

Updated information is provided **in** the l**atest** RO5520985 IB.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Current first- and second-line therapies for mCRC include a variety of different oxaliplatin- and irinotecan-based chemotherapy regimens, including FOLFOX and FOLFIRI which have similar activity, but different toxicity profiles. Improved outcomes have been demonstrated with chemotherapy combined with therapies targeting the EGFR or VEGF(R) pathway (Van Cutsem et al. 2010). In particular, the addition of bevacizumab, a recombinant humanized anti–VEGF-A mAb, to standard chemotherapies for mCRC has been shown to improve overall and progression-free survival, as well as response rates (Grothey and Allegra 2012). Hence, the success of anti–VEGF-A therapy provides the basic rationale to explore treatment options that additionally target key angiogeneic pathways that could further improve upon the clinical benefit of bevacizumab.

The VEGF pathway and the Angiopoietin/Tie2 receptor axis have distinct complementary roles in the regulation of tumor angiogenesis, vascular permeability and tumor progression; however, compensatory alternative angiogenic pathways are potential mechanisms of tumor escape that likely limit the full potential of anti-angiogenic monotherapies. Ang-2 expression has been shown to function as a key regulator of tumor angiogenesis and metastasis in colorectal cancer. Upregulation of Ang-2 is associated with tumor invasiveness, adverse prognosis and poor clinical outcome of patients with mCRC treated with bevacizumab containing therapy (Chung et al. 2006). Recent data have demonstrated that Ang-2 inhibitors, both as single agents or in combination with anti-VEGF therapy exert anti-tumor activity in preclinical CRC models (Hashizume et al. 2010; Brown et al. 2010; Coxon et al. 2008) and interfere with metastasis formation (Mazzieri et al. 2011).

RO5520985 (Ang-2/VEGF-A CrossMab) is a novel bevacizumab-based bispecific human IgG1 antibody acting as a dual-target inhibitor of the two key angiogenic factors VEGF-A and Ang-2. The Ang-2/VEGF-A CrossMab showed potent tumor growth inhibition in a panel of orthotopic and subcutaneous syngeneic mouse tumors and patient or cell line derived human tumor xenografts, especially at later stages of tumor development (Kienast et al. 2013). In a Colo205 colorectal cancer tumour xenograft model, RO5520985 demonstrated superior efficacy (as assessed by TGI) versus the single agent inhibitors of VEGF-A and Ang-2. Additionally, metastatic tumor cell spread (through leaky vessels) to the lung was reduced by Ang-2/VEGF-A CrossMab within the

same model. Interestingly, RO5520985 also showed superior anti-tumor activity on larger tumors compared with the monotherapies, supporting the notion that larger tumors consist of different vessel types that do not all respond equally to anti-VEGF-A therapy (Nagy and Dvorak 2012). With regards to the clinical situation, RO5520985-induced tumor vessel normalization in various models and had superior anti-tumor activity in combination with chemotherapy (docetaxel) vs. bevacizumab plus docetaxel or docetaxel alone in an orthotopic KPL-4 breast cancer model, indicative of an improved delivery of the cytotoxic combination partner within the tumor tissue (Kienast et al., 2013).

To date, the observed clinical safety profile of single agent RO5520985 (ClinicalTrials.gov, NCT01688206) has been consistent with that reported for bevacizumab and other inhibitors of the Ang/Tie-2 axis administered to patients with advanced solid tumors, **however the incidence rates of arterial hypertension and GI-perforation associated with the use of RO5520985 seems to be higher than those reported for bevacizumab.** RO5520985 also appears to impact tumor vascularity and showed encouraging anti-tumor activity in this heterogeneous patient population. The medical need for prospective clinical trials to further optimize the standard treatment of metastatic CRC is well recognized and supported by current therapy guidelines (NCCN Guidelines Version 2.2014). The purpose of this study is to determine if concurrent target inhibition of the VEGF-A and Ang-2 axis by addition of the bispecific mAb RO5520985 to standard chemotherapy can improve the outcome of patients with metastatic CRC.

In Part III of the phase 1 study BP28179 of single agent RO5520985 in patients with epithelial ovarian, fallopian tube or primary peritoneal cancer, 5 of 41 patients (12.2%) developed GI perforation (GIP). Two of these patients had a fatal outcome. GI perforation is an identified risk for RO5520985, however, this incidence exceeds what has been reported with bevacizumab in ovarian cancer.

As of the cut-off date (27-Nov 2015) in this study BP29262, the incidence of GIP events (including perforation, intra-abdominal abscess, and GI fistula) was 11.1% (8/72 patients) in Arm A versus 5.6% (4/71 patients) in Arm B. The GIP events in Arm A included a colon perforation following colonoscopy the day before the event and a colonic prosthesis perforation. Likewise, a GI tumor perforation in Arm A was assessed as unrelated to blinded vanucizumab (RO5520985)/ bevacizumab, but as related to a prosthetic breakage. A non-serious GIP event of bowel micro-perforation occurring in Arm A did not require patient hospitalization. One GIP in Arm A had a fatal outcome in a [redacted]-year old [redacted] patient. GIP is an identified risk for RO5520985/ bevacizumab, however, particularly the reported incidence in Arm A of BP29262 exceeds what has been reported with bevacizumab in CRC which ranges from 1 to 4 % across treatment lines. Several clinical risk factors have been postulated to increase the risk of bowel perforation from bevacizumab in metastatic CRC, including a history of peptic ulcer disease, diverticulitis/colitis, intestinal obstruction, tumor necrosis, recent sigmoido-

/colonoscopy, stent implants, intact primary tumor, radiotherapy, higher cumulative dose of bevacizumab, or emergent surgery while receiving bevacizumab (Abu-Hejleh et al 2012; Imbulgoda et al 2015). In response to the GI-perforation events, additional risk mitigation measures have been introduced into study BP29262 (Section 4.2.3 and Section 5.2.3.2). In conclusion, inhibiting tumor angiogenesis by dual blockade of the VEGF-A and Ang-2 pathway may represent a novel approach for cancer treatment. The supportive preclinical data set in conjunction with an encouraging, preliminary clinical experience of RO5520985, **have** provide**d** a favorable benefit-risk balance for a further clinical investigation of RO5520985 in cancer. **In regards to the observed GI-perforation rate, the proposed risk mitigation plan supports the continuation of study BP29262 while closely monitoring all patients for clinical signs and symptoms suggestive of intestinal sub-/occlusion/intestinal obstruction or GI-perforation.**

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of Study BP29262 is to estimate the efficacy of RO5520985 in combination with oxaliplatin, folinic acid, and 5-fluorouracil (mFOLFOX-6) vs. bevacizumab in combination with mFOLFOX-6, as measured by progression-free survival (PFS).

2.2 SECONDARY OBJECTIVES

- Evaluate the safety and tolerability of RO5520985 in combination with mFOLFOX-6
- Estimate the efficacy of RO5520985 in combination with mFOLFOX-6, as measured by overall survival, objective response rate, and duration of objective response
- Characterize the pharmacokinetics of RO5520985 when combined with mFOLFOX-6

2.3 EXPLORATORY OBJECTIVES

- Assess levels of circulating angiogenic factors and circulating targets as potentially predictive markers, in conjunction with somatic mutations in circulating cell-free DNA
- Assess potential response prediction markers of RO5520985 in blood and archival primary tumor tissue
- Characterize the PK of selected mFOLFOX-6 components when combined with RO5520985
- Explore tumor growth kinetics
- Explore additional parameters on tumor imaging

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase II, multicenter, randomized, parallel arms, double-blind study of RO5520985 to evaluate the efficacy and safety of RO5520985 plus mFOLFOX-6 versus bevacizumab plus mFOLFOX-6 in patients with previously untreated mCRC. The study consists of two parts: Part I (Safety Run-in) open label single arm and Part II (Randomization Phase) randomized, parallel arms, double-blind study.

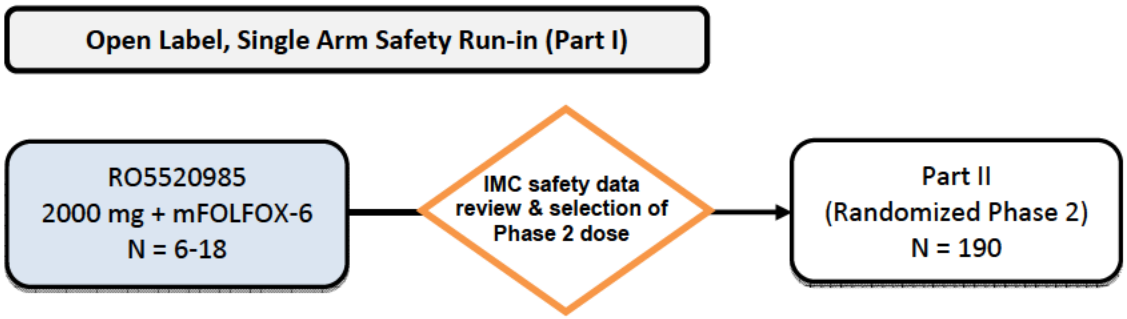
3.1.1.1 Part I: Safety Run-in

The safety/ tolerability of single agent RO5520985 has been investigated in Study BP28179, by which RO5520985 at 2000 mg Q2W was considered safe and recommended as dose for subsequent clinical development. However, the combination of RO5520985 with mFOLFOX-6 has not been previously studied clinically for safety. Therefore, during the open label safety run-in phase prior to the randomization part of the study (Part II) at least 6 eligible patients will be exposed to 2000 mg Q2W RO5520985 + mFOLFOX-6, in order to confirm the dose and schedule that will be used in the randomized part of this study (Part II). All patients in Part I will receive induction and maintenance therapy as described for patients in the experimental arm of Part II. Treatment of the first 6 patients will be sequential i.e., there will be always at least 1 working day between the 1st RO5520985 administration of one enrolled patient and the 1st RO5520985 administration of the next enrolled patient.

Each site enrolling one of the first 6 patients in Part I needs to inform the Sponsor about the tolerability (based on the assessments being performed as per SoA) by e-mail. The e-mail needs to be send after the investigator or designee has seen the patient during the Visit on Day 2 of Cycle 1 reporting at least the observed AEs/SAEs between start of RO5520985 administration and the Visit on the next day (C1D2). Only after confirmation by the site that the 1st study drug administration was tolerated without any severe problems, the next patient can be treated. The Sponsor ensures that the site enrolling the subsequent patient will be informed latest on the evening prior to the scheduled treatment whether the patient can receive the 1st RO5520985 administration.

After at least 6 patients have been treated by at least two full cycles, an Safety Internal Monitoring Committee (IMC) will conduct a safety analysis prior to initiation of Part II. If safety signals arise from the review and depending on the nature of the safety signals, the Safety IMC may recommend to enroll additional 6-12 patients at lower doses of RO5520985 in combination with mFOLFOX-6 before embarking onto Part II of the study at the adjusted dose. In case of unacceptable and/or non-manageable toxicity of the combination, the Safety IMC may decide to discontinue the study upon completion of Part I, The Safety IMC will operate according to a prespecified safety charter outlined in a separate document. Further details are provided in Section 3.1.2. A schema of the safety run-in is provided in Figure 1.

Figure 1 Part I – Safety Run-in

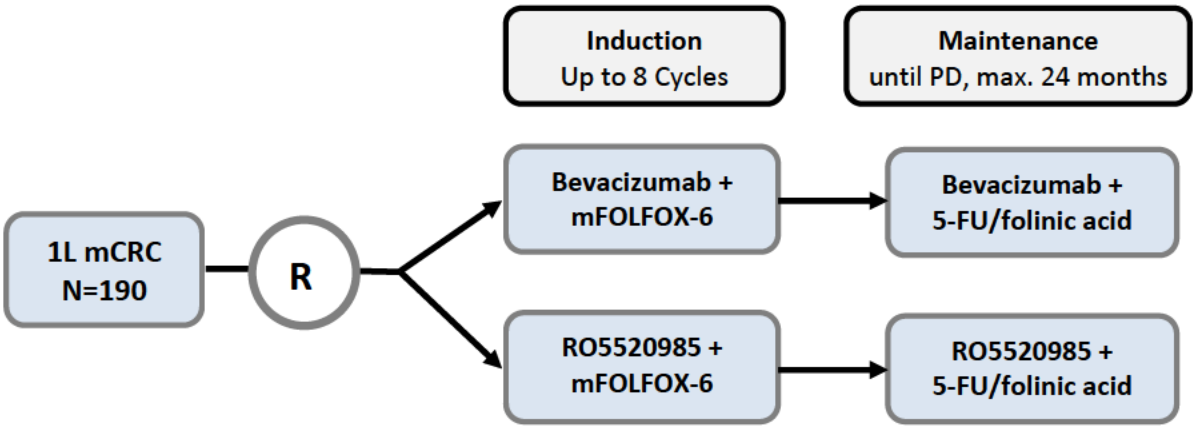


mFOLFOX-6 = 5-FU, leucovorin, and oxaliplatin; RP2D = recommended Phase 2 dose.

3.1.1.2 Part II: Randomization Part

Upon completion of the safety run-in part with selection of the RP2D of RO5520985 in combination with mFOLFOX-6 by the Safety IMC, eligible patients will be randomized in a ratio of 1:1 to receive either mFOLFOX-6 + RO5520985 (experimental arm) or mFOLFOX-6 + bevacizumab (control arm). A schema of the randomization part is provided in Figure 2.

Figure 2 Part II – Randomization Part



5-FU = 5-fluorouracil; DP = disease progression; mCRC = metastatic colorectal cancer; mFOLFOX-6 = 5-FU, leucovorin, and oxaliplatin; R = randomization.

Patients will prospectively be stratified by region (United States vs. Rest of World [RoW]) and number of metastatic sites (1 vs. > 1).

Study treatment

Study treatment consisting of induction and maintenance therapy will be given in cycles repeated every 14 days.

a) Induction therapy

Up to 8 cycles of mFOLFOX-6 plus either bevacizumab or RO5520985. Patients may switch to maintenance therapy earlier if oxaliplatin cannot be tolerated.

b) Maintenance therapy

Following induction therapy, oxaliplatin administration will be discontinued and patients receive 5-FU/folinic acid plus either RO5520985 (experimental arm) or bevacizumab (control arm) as maintenance therapy for a maximum period of 24 months (calculated from start of maintenance therapy), if treatment is not stopped earlier due to disease progession, unacceptable toxicity, Investigator decision or consent withdrawal. If patients stop chemotherapy either in part or in whole, then they should continue on RO5520985 treatment or bevacizumab for a maximum of 24 months.

Within Part II of the study, two interim analyses are planned (Section 6.10) which will be conducted by an Efficacy IMC.

3.1.2 Internal Monitoring Committee

There will be two separate Internal Monitoring Committee (IMC) – one for safety and one for efficacy.

The Safety Internal Monitoring Committee (IMC) will be composed of at least a Sponsor translational medicine leader/clinical scientist, safety scientist/safety science leader, statistical programming analyst (SPA) and biostatistician and will operate according to a prespecified safety charter outlined in a separate document. The primary responsibilities of the Safety IMC will be to review the available safety data and to make a recommendation to continue, modify, or terminate the study based on the safety data.

A safety analysis will be conducted by the Safety IMC after at least 6 patients in Part I have been treated for at least two full cycles RO5520985 at 2000 mg Q2W plus mFOLFOX-6. If safety signals arise from the review and depending on the nature of the safety signals, the Safety IMC may recommend to enroll additional 6-12 patients at lower doses of RO5520985 in combination with mFOLFOX-6 before embarking on into Part II of the study. In case of unacceptable safety/toxicity of the combination, the Safety IMC may also decide to discontinue the study upon completion of Part I.

In accordance with the charter, the Safety IMC may also conduct further blinded safety reviews based on safety signals that arise at any time during Part II of the study. In this case, the randomization code will be received by an unblided programmer at the CRO and the study statistician and statistical programmer will receive the unblinded data which will be saved in a restricted area. Accrual will not be halted while the analysis is being conducted. Outcomes and conclusions of the IMC that affect study conduct will be communicated to the U.S. FDA and other regulatory agencies, as well as

the Investigators for notification of the IRBs/ECs as soon as possible and no more than 15 days after the analysis is completed.

Separate from the Safety IMC, there will be in addition an Efficacy IMC responsible for the futility/efficacy analysis of Part II. The details and modalities are described in a pre-specified charter outlined in a separate document as well as in the statistical analysis plan.

3.1.3 End of Study

After the completion of induction therapy patients will continue maintenance therapy for a maximum of 24 months unless the occurrence of disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision. All patients will attend a safety visit 5 ($\pm$1) weeks after receiving the last administration of RO5520985, which is the End of Study (EoS) Visit. Patients off study will receive standard of care for the stage of their disease. Follow-up for survival will continue until all patients have either died or are lost to follow up, or the sponsor decides to end the trial, whichever occurs first.

The study will formally end once the survival follow-up is complete or the last patient has completed the EoS Visit or is withdrawn from the study prior to that time (whichever occurs last), but may be prematurely terminated by the Sponsor. The main analysis and reporting will be conducted once approximatelly 80 PFS events have been collected, When the study is formally ended, an additional analysis will be performed and appended to the main report.

3.1.4 Study Duration

The time needed for study enrollment is estimated to be approximately 15 months. The total duration of the study for each patient will be as follows:

- Screening: Up to 4 weeks
- Treatment period: Patients will receive induction therapy for up to 8 cycles (approximately 4 months), followed by maintenance therapy for a maximum of 24 months unless the occurrence of disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision require treatment cessation.
- EoS Visit: Up to 6 weeks (5 $\pm$ 1 weeks) after last dose of RO5520985
- Post study human anti-human antibody (HAHA) Visit (optional): 2 months ($\pm$2 wks) after last dose of RO5520985
- Post study follow-up: All patients will be followed for survival (e.g., by phone call or clinic visit) and subsequent anticancer therapy approximately every 3 months after EoS Visit until death, loss to follow-up, or study termination by Roche, whichever occurs first

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Selection of RO5520985 Dose and Schedule

The dose selection of RO5520985 was based on clinical safety/tolerability, efficacy, pharmacodynamic (incl. functional imaging) and pharmacokinetic data obtained from a Phase I entry in human study (BP28179). Within this study escalating doses of RO5520985 were evaluated in 42 patients using either a weekly (QW: 10, 20, and 30 mg/kg) or bi-weekly (Q2W: 3, 6, 12, 19.2 and 30 mg/kg) dosing schedule, with 30 mg/kg being the highest dose level tested. The preliminary safety and tolerability profile of RO5520985 has been comparable between QW and Q2W regimens and comparable to bevacizumab. Consistent with the mode of action of a VEGFA-inhibitor, arterial hypertension (HTN) was the most frequent adverse event across all dose levels, with a higher incidence of grade 3 HTN associated with the weekly regimen (30% vs. 9%). However, a MTD was not reached in either dosing schedule. Based on small numbers, increased clinical activity, assessed by the progression-free rate at 8-weeks, was observed with escalating doses of RO5520985, reaching its maximum of 83% at 30 mg/kg Q2W. The PK profile of RO5520985 exhibited dose proportionality across the entire dose range studied (3–30 mg/kg), with an elimination half-life of approximately 7–9 days, based on a Q2W dosing schedule. Population PK analysis indicated that biweekly dosing of 30 mg/kg results in C_{trough} and C_{avg} of RO5520985 plasma levels (by the 2nd cycle) that are comparable to 5 mg/kg Q2W bevacizumab, which is a standard dose in combination with chemotherapy (incl. FOLFOX) for the treatment of mCRC. Exploratory functional imaging (i.e., DCE-/DW-MRI) analysis indicated vascular effects across the dose levels and schedules tested in 22 of 34 evaluable patients; however, within the biweekly schedule sustained decrease in vascular characteristics (e.g., vessel permeability) and increased on-treatment necrosis appeared to be associated with 30 mg/kg Q2W.

Fixed dosing regimens have been recommended as the preferred dosing approach as it offers considerable advantages in the ease of dose preparation and thereby avoid potential dose calculation errors (Mathijssen et al. 2007, Wang et al. 2009). The PK profile and key PK parameters (C_{max}, AUC) of RO5520985 demonstrated a low (< 30%) inter-individual variability for both dosing schedules. Based on an average 70 kg patient, a dose of 30 mg/kg approximates to a flat dose of 2100 mg. Further simulations of repeated administration of both body weight normalized (30 mg/kg) and flat (2000 mg) doses of RO5520985 Q2W indicated that the steady-state systemic exposures, peak and trough concentrations would be comparable for the two dosing strategies, with similar inter-individual variability. Hence, flat-fixed dosing of RO5520985 will provide consistent exposure across patients and has been proposed for the subsequent clinical development.

Based on these considerations, it was concluded that RO5520985 at 2000 mg Q2W is a clinically feasible dosing regimen that has an acceptable safety profile and is potentially active when combined with chemotherapeutic agents for the treatment of cancer.

3.2.2 Rationale for Safety Run-in (Part I)

Monoclonal antibodies inhibiting angiogenesis provide modes of action, metabolism and clinical toxicity profiles different from traditional chemotherapy agents. The safety profile of bevacizumab in combination with various chemotherapies is well characterized in randomized clinical trials and by data from clinical practice. Bevacizumab is associated with increases in the frequency of AEs that are seen with essentially all VEGF-A inhibitors, such as hypertension, proteinuria, and thromboembolic events (Hurwitz et al. 2013; Mohile et al. 2013). With few, if any, overlapping toxicities with traditional chemotherapies, the primary side effect of bevacizumab is hypertension what can easily be managed, requiring the addition or adjustment of oral anti-hypertensives in approximately 11% of patients (Hurwitz et al. 2005). Clinical experience with inhibitors of the Angiopoetin/Tie-2 axis, in combination with common chemotherapy regimens and bevacizumab has revealed acceptable safety profiles with manageable toxicity consistent with prior experience with individual treatments (Mita et al. 2010; Peeters et al. 2013; Dieras et al. 2011). The safety of single agent RO5520985 has been investigated in Study BP28179, showing an acceptable toxicity profile consistent with that reported for bevacizumab and other inhibitors of the Ang/Tie-2 axis. However, the combination of RO5520985 (2000 mg Q2W) with conventional chemotherapy has not been previously explored for safety in the clinic. Hence, for the utmost safety of study patients, the safety run-in phase (Part I) (Section 3.1.1.1) will first determine the RP2D of RO5520985 in combination with mFOLFOX-6 in at least six previously untretated patients with mCRC before embarking on Part II.

3.2.3 Rationale for Randomized, Double-blind Phase II Study in First-line mCRC (Part II)

Despite recent improvements with the addition of bevacizumab to standard oxaliplatin-based treatment regimens, median survival for patients with mCRC is still approximately 20 months (Hurwitz et al. 2004), leaving a significant unmet need for more efficacious treatments. Hence, prospective clinical trials to further optimize the standard treatment of metastatic colon cancer are needed and supported by current therapy guidelines. The randomized Phase II design (Part II) of this study will allow to accurately assess the anti-tumor activity of RO5520985 plus mFOLFOX-6 ('Experimental Arm') compared to the Standard of Care (SoC) of bevacizumab plus mFOLFOX-6 ('Control Arm') as first-line treatment of mCRC. RO5520985 is a novel bevacizumab–based bispecific mAb acting as a dual-targeting inhibitor of the two key angiogenic factors, VEGF-A and Ang-2. Thus, patients who are randomized to the 'Experimental Arm' may experience additional clinical benefit by concurrent Ang-2/VEGF-A inhibition. In view of the potential importance of continuing biological therapy until disease progression and minimizing early treatment discontinuation due to chemotherapy-related toxicity, patients in this study will receive oxaliplatin for a maximum of 8 cycles during the induction phase and can subsequently stay on a well tolerated 5-FU plus RO5520985 or bevacizumab based maintenance therapy until documented disease progression or unacceptable toxicity for a maximum of 24 months.

3.2.4 Rationale for Biomarker Assessments

The efficacy of bevacizumab has been demonstrated in several randomized controlled trials in colorectal cancer. However, so far the attempts to identify a patient population that might benefit most from the combination of bevacizumab with standard therapy have failed to define any specific patient subgroup. Still, ongoing research aims to identify a predictive biomarker or combination of biomarkers enabling selection of patients that would benefit most from bevacizumab therapy .

The main objective of the biomarker analyses is to identify biomarkers for prospective selection of patients who are most likely to respond to RO5520985 treatment. Therefore, biomarker data will be correlated with clinical outcome. This assessment will be performed in archival primary tumor tissue and in blood samples. A pharmacodynamic analysis will be done for the targets, Ang-2 and VEGF-A to confirm MoA and for PK/PD correlation. PlGF (placental growth factor) might be a pharmacodynamic (PD) marker of endothelial response towards anti-angiogenic treatment, therefore on-treatment samples will also be analyzed for PlGF (Xin et al. 2012).

Patients will be asked for collection of additional blood samples to be stored in the Roche Clinical Repository (RCR).

3.2.4.1 Biomarker Assessments in Blood

The objective of the biomarker analyses in plasma is to quantify the levels of circulating targets and other angiogenesis-relevant factors for predictive hypothesis generation.

3.2.4.1.1 Pharmacodynamic markers

Angiopoietin-2 (Ang-2) and VEGF-A: Ang-2 and VEGF-A are the targets for RO5520985. Soluble Ang-2 **potentially** has prognostic/predictive value in patients who have CRC treated with bevacizumab (Goede et al. 2010; Liu et al. 2013) and may therefore have positive predictive potential for treatment responders. In addition both targets will be analyzed at various timepoints on treatment (Schedule of Assessments [SoA], Appendix 1). This enables the confirmation of the expected results in Phase I where decreased levels of biologically active, free (nondrug bound) Ang-2 and VEGF-A and increased concentrations of total (free plus drug bound) Ang-2 and VEGF-A were observed. The assessment of their value as PD and/or possible resistance markers might help to discriminate between bevacizumab and RO5520985 treatment effects in a larger, more homogenous patient population.

Placental growth factor (PlGF): PlGF showed sustained upregulation following various treatments such as bevacizumab, SU11248, AZD2171 (Horowitz et al. 2011, Loupakis et al. 2011; Deprimo et al. 2007; Xin et al. 2012) and in the ongoing Phase I trial of RO5520985. The analysis of the induced changes during treatment may help to discriminate between bevacizumab versus RO5520985 induced effects.

Circulating tumor DNA (ctDNA): Circulating tumor DNA potentially predicts treatment response and early disease progression as somatic genetic alterations in most cancers and specifically in CRC represent molecular signatures. Following an initially broader mutational analysis of the primary tumor tissue DNA, specific mutation(s) will be analyzed in the baseline and on-treatment plasma samples (Pantel and Alix-Panabières 2013; Diehl et al. 2005). So far there are only few reports on the use of ctDNA in CRC, so our data will provide an understanding of the value of liquid biopsies in a clinical setting in general and specifically in first-line treatment of mCRC patients.

3.2.4.1.2 Predictive Biomarkers

Besides the possible predictive value of Ang-2, VEGF-A and PlGF (see above) we will assess the markers detailed below.

Angiopoietin-1 (Ang-1), Matrixmetalloproteinase-2 (MMP-2) and Matrixmetalloproteinase-9 (MMP-9): Ang-1 is expressed by pericytes, smooth muscle cells and fibroblasts and functions as a strong Tie2 agonist. Ang-1 regulates vascular maturation and stabilization by maintaining endothelial cell survival and quiescence in mature vessels. Ang-1 and Ang-2 are thought to act mainly in an antagonistic manner, though Ang-2 has the potential to activate or inactivate Tie-2 in certain contexts (Koh 2013). Considering this potential antagonistic relationship, Ang-1 might have a predictive value for therapeutic Ang-2 inhibition. MMP-2 and MMP-9 play a role in cancer progression and metastasis and are both involved in angiogenesis. MMP-2 knockout mice show impaired angiogenesis whereas MMP-9 is involved in the angiogenic switch of tumor cells (Itoh et al. 1998; Bergers et al. 2000; Mook et al. 2004; Roy et al. 2009). The study will assess whether Ang-1, MMP-2 and/or MMP-9 will be predictive for RO5520985 in CRC.

Additional angiogenesis-related markers: Various angiogenesis-related markers will be assessed at baseline to evaluate their predictive value in CRC patients receiving anti-angiogenic treatment. In case of an emerging predictive marker, its potential to differentiate between bevacizumab and RO5520985 treatment will be determined. The following exploratory markers will be assessed: sTie-2, VEGF-C, sVEGF-R1, sVEGF-R2, sVEGF-R3, SDF-1α, E-selectin, ICAM-1, bFGF, IL-8, PDGF-C, and CA-IX.

3.2.4.2 Archival Primary Tumor Tissue

Collection of archival primary tumor tissue is mandatory. The objective of tumor tissue biomarker analyses is to assess the targets of RO5520985, vessel– and tumor cell–related parameters and tumor-infiltrating immune cells.

Targets and Receptors: Analyses are performed to assess if different vessel subtypes respond differently to RO5520985 therapy. For example, it is hypothesized that Ang-2 positive vessels are more likely to be affected by treatment with RO5520985 than Ang-2 negative vessels. In addition, the expression of the RO5520985 targets may be associated with response to treatment. The prevalence of Ang-2 expression in CRC

tissue is 86% according to own data. High tissue Ang-2 levels correlate with worse clinical outcome and have been shown to drive lymphatic metastasis in breast cancer and pancreatic cancer (Sfiligoi et al. 2003; Etoh et al. 2001; Ochiumi et al. 2004).

VEGF: VEGF-A as a possible tissue biomarker has been assessed in three trials using anti-VEGF-A therapy in CRC. In the first-line mCRC trial Study NO16966, higher levels of tumor VEGF-A were associated with improved PFS, though the quality of immunohistochemistry (IHC) was questionable (Foernzler et al. 2010), whereas two other trials with mCRC patients (Studies AVF2107 and ML18147) could not show any correlation of tissue VEGF-A and clinical outcome (Jubb et al. 2006; Kubicka et al. 2013). Still the predictive value of tissue VEGF-A using RO5520985 in CRC has not been assessed so far. VEGF-R2 is the primary receptor that promotes the pro-angiogenic function of VEGF-A (Carmeliet et al. 2001) and will be analyzed as well.

Vessel-related parameters: MVD, proliferation and apoptosis in endothelial cells and maturity of blood vessels will be determined. In bevacizumab-treated patients who have CRC, immature blood vessels have been shown to correlate with poor survival (Noonan et al. 2011) and high MVD was prognostic in ovarian cancer patients (Rubatt et al. 2009). Within the study a reduction of MVD and EC proliferation together with an increased maturity of remaining blood vessels (Willet et al. 2004, Willet et al. 2005, Wedam et al. 2006) during RO5520985 therapy is expected. Therefore parameters indicating active angiogenesis such as high MVD and high percentage of immature blood vessels, might have predictive value in CRC patients. The following markers will be assessed: CD31, CD34, Podoplanin, αSMA. The analysis will be prioritized based on the amount of material available.

Tumor cell-related parameters: Markers reflecting the tumor status such as proliferation and hypoxia will be explored. High Ki67 expression is in general associated with higher tumor activity, higher histopathological grading and poorer course of disease. CAIX is a marker of hypoxia and high stromal expression has been shown to be prognostic in a few tumor entities (Klimowicz et al. 2013; Brockten et al. 2012). The predictive value of Ki67, CA-IX, c-C3, and neuropilin-1 will be explored.

Tumor-infiltrating immune cells: The role of tumor-infiltrating macrophages in CRC is still controversial and there are reports of a better prognosis and survival rate associated with a high number of macrophages (Zhou et al. 2010; Funada et al. 2003; Khorana et al. 2003) as well as their association with greater depth of tumor invasion, lymph node metastasis, and staging (Kang et al. 2010; Pancione et al. 2009; Deschoolmeester et al. 2011). Besides macrophages, the immune contexture of the tumor has a major clinical impact for prognosis, such as for example the high number of infiltrating T cells in CRC (Pages et al. 2005; Galon et al. 2006). The immune contexture is generally thought as a major element to establish the prognosis of patients and guide therapy, though it is not expected to be as informative in metastatic disease as in lower stages (Fridman et al. 2012; Galon et al. 2006). An additional aspect looking at tumor-infiltrating immune cells

is the observation that Ang-2 overexpression in tumor tissue enhances the infiltration of Tie2-expressing macrophages/monocytes via Tie-2 signaling and augments leukocyte extravasation in inflamed tissue (De Palma and Naldini 2011).

To test the response predictive value of tumor-infiltrating immune cells we will assess (but it is not limited to) CD4, CD8, CD3, CD68/CD163, CD3/FOXP3, CD3/perforin. The analysis will be prioritized on the basis of the amount of material available. Broader analysis will be performed using a gene expression analysis technology to assess changes at the molecular level.

Mutational analysis: In CRC several DNA mutations caused by genomic instability, chromosomal aberrations, and DNA promotor hypermethylation have implications on prognosis (Cancer Genome Atlas Network 2012; Simons et al. 2013). Besides mutated *RAS* and *BRAF* being predictive for anti-EGFR (epidermal growth factor receptor) treatment in CRC (Lievre et al. 2006), other genes such as *PI3KCA* [Samuels and Ericson 2006, Liang et al. 2003), *PTEN* (Tol et al. 2010; Bardelli and Siena 2010) and the microsatellite instability (MSI) status (Lothe et al. 1993; Popat et al. 2005) have been associated with clinical outcome. Therefore, a broader exploratory mutational analysis including, but not limited to*:* KRAS, NRAS, EGFR, BRAF, PI3KCA, PTEN, MET, APC will be performed. Additionally, KRAS and NRAS mutational analyses will be used for retrospective sub-group analyses.

In case a new predictive biomarker for anti-angiogenesis treatment with the potential to differentiate between anti-VEGF-A and anti-Ang-2/VEGF-A treatment is identified in the future, further analysis will be performed using the available samples. Therefore, patients will be asked for specific consent for remaining plasma samples to be stored in the Roche Clinical Repository (Section 4.6.1.15) for future research.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03
- Changes in hematology, biochemistry, coagulation, specifically those associated with vascular and renal function
- Physical examinations (including ECOG), vital signs and ECG
- Incidence and titers of human anti-human antibodies (HAHAs)
- Adverse events leading to RO5520985, bevacizumab, or chemotherapy discontinuation

- Incidence of the following selected adverse events according to NCI CTCAE, v4.03:
  - Arterial hypertension (Grade ≥3)
  - Proteinuria (Grade ≥3)
  - Arterial thromboembolic events (any grade)
  - Venous thromboembolic events (Grade ≥3)
  - Vascular disorder - other: Thrombotic microangiopathy (any grade)
  - Gastrointestinal perforation (any grade)
  - Fistula involving an internal organ (any grade)
  - Fistulae (Grade 4)
  - Wound healing complication (Grade ≥3)
  - Bleeding/hemorrhage (Grade ≥3)
  - Pulmonary bleeding (Grade ≥2)
  - CNS bleeding (Grade ≥2)
  - Congestive heart failure (Grade ≥3)
  - Reversible posterior leukoencephalopathy syndrome (any grade)

3.3.2 Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are as follows:

- The PK profile of RO5520985 will be characterized with the plasma concentration-time data following IV administration of RO5520985, and will include the following parameters: C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC, AUC_{τ}, CL, V_{ss}, accumulation ratio (RA)
- The PK profiles of oxaliplatin (free and total) and 5-FU will be characterized with the plasma concentration-time data following IV administration of FOLFOX, and will include the following parameters: C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC (when applicable)
- Additional PK parameters may be evaluated as appropriate

3.3.3 Efficacy Outcome Measures

The primary and secondary efficacy analyses will be based on the efficacy analyses population, which includes Part II patients only. Efficacy for Part I patients will be analyzed using descriptive statistics.

3.3.3.1 Primary Outcome Measure

The primary outcome measure for Study BP29262 is progression-free survival, defined as the time from randomization to the date of first documented occurrence of progression based on RECIST v1.1 criteria (Appendix 8) as determined by the Investigator or death from any cause on study, whichever occurs first.

3.3.3.2 Secondary Outcome Measures

The secondary outcome measures for Study BP29262 are as follows:

- Objective response rate (ORR). Objective response rate is defined as the rate of patients with an objective tumor response, i.e. partial response (PR) or complete response (CR) as determined by the Investigator using RECIST v1.1 criteria on two consecutive occasions at least 4 weeks apart.
- Duration of response, defined as the first occurrence of a documented objective response until the time of progression or death from any cause on study
- Overall Survival, defined as the time from randomization until death from any cause

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures for both Part I and Part II of the study include but are not limited to the following:

- Levels of circulating targets by comparing baseline vs. on-treatment values of Ang-2 and VEGF-A and their differential expression/regulation during RO5520985 versus bevacizumab therapy
- Changes of PlGF from baseline during treatment as marker of unspecific endothelial stress response and as potential response towardsRO5520985
- Assessment of tissue and soluble blood markers potentially related to predicting clinical benefit or toxicity of RO5520985 vs. bevacizumab
- An assessment of tumor growth kinetics will be made by comparing post-treatment scans with at least 2 pre-treatment scans not older than 12 weeks prior to C1D1, if available. The two pre-treatment scans consists of a pre-study scan and the study baseline scan.
- Analysis of additional CT parameters including necrotic volume/total tumor volume and intensity to assess their potential value as early response prediction markers

4. MATERIALS AND METHODS

4.1 CENTERS

This is a multi-center study. Approximately 50 sites in approximately 7-10 countries will participate in the study. Additional sites may be included as back-up and activated as appropriate.

Administrative and Contact Information, and List of Investigators are provided separately.

4.2 STUDY POPULATION

Adult patients (≥18 years) with mCRC who have not been previously treated with chemotherapy for metastatic disease and who are not candidates for potentially curative resection.

4.2.1 Recruitment Procedures (Part I and Part II)

All patients must provide written informed consent before any study specific assessments or procedures are performed. Once the patient has signed the informed consent, the Investigator (or his designee) contacts the IxRS to perform a screening call for the patient. The site will then be provided with a screening number. An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed and signed by the Investigator (or designee). A patient Enrollment and Identification Code List must also be maintained by the Investigator. Patients who fulfill all of the inclusion criteria and none of the exclusion criteria are eligible to participate in the study. The site uses the IxRS to obtain a patient number. The process is described in Section 4.3.

Patients who enroll and subsequently discontinue from this study are not permitted to enroll again into this trial.

4.2.2 Inclusion Criteria

Patients eligible for inclusion in this study for both Part I and Part II have to meet all of the following criteria:

1. Histologically or cytologically confirmed mCRC not amenable to potentially curative resection with at least one measurable metastatic lesion, as defined by RECIST v1.1 (Appendix 8)
   a) Representative tumor specimens in FFPE blocks (preferred) or slides must be available for central extended RAS mutational analysis
2. Signed written informed consent, obtained prior to any screening procedure
3. Age ≥ 18 years
4. ECOG (WHO) performance status of 0 or 1 (Appendix 5)
5. Willing and able to comply with the protocol as judged by the Investigator
6. Adequate hematologic function
   a) Absolute neutrophil count (ANC) ≥ 2000 cells/μL (without G-CSF [granulocyte colony-stimulating factor] support within 2 weeks prior to randomization)
   b) Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to randomization)
   c) Hemoglobin ≥ 9.0 g/dL
7. Adequate liver function
   a) AST and ALT ≤ 2.5 × upper limits of normal (ULN) or ≤ 5 x ULN in case of liver metastases
   b) Serum bilirubin ≤ 1.5× ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled
   c) Serum albumin ≥ 3.0 g/dL

8. Adequate coagulation function
    a) International normalized ratio (INR) ≤ 1.5 × ULN
    b) Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
9. Adequate renal function
    a) Creatinine clearance ≥ 50 mL/min/1.73 m^2 on the basis of the Cockroft–Gault formula (Appendix 4)
    b) Urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hrs urine collection and must demonstrate ≤ 1 g of protein in 24 hrs before starting of dosing
10. Adequate cardiovascular function
    a) NYHA stage ≤ 1 (Appendix 6)
    b) Resting blood pressure systolic < 150 mmHg and diastolic < 100 mmHg (average of ≥ 3 readings on ≥ 2 sessions)
11. Recovery from all reversible adverse events of previous medical therapies to baseline or NCI CTCAE Grade 1, except for alopecia (any grade)
12. Negative serum or urine pregnancy test within 7 days prior to starting study treatment in premenopausal women and women < 2 years after the onset of menopause

4.2.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Any prior systemic therapy (including chemotherapy, antibody therapy, tyrosine kinase inhibitors, immunotherapy, hormonal therapy) before Day 1 of Cycle 1 for treatment of mCRC
    a) Patients who received prior systemic adjuvant therapy or radiotherapy for CRC are not excluded if the time interval from last administration of adjuvant therapy until disease progression is > 12 months
    b) Patients who received herbal therapy intended as anti-cancer therapy ≥ 2 weeks prior to Day 1 are not excluded
2. Malignancies other than CRC within 5 years prior to randomization, except for those with a minimal risk of metastasis or death, such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ treated surgically with curative intent
3. **R**adiotherapy within 28 days **and abdominal/ pelvic radiotherapy within 60 days** prior to Day 1 of Cycle 1, except palliative radiotherapy to bone lesions within 7 days prior to Day 1 of Cycle 1
4. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to Day 1 of Cycle 1
5. Pregnant or lactating women
6. Known hypersensitivity reaction to any study medication (or excipients).

7. Any disorder that compromises the ability of the patient to provide written informed consent and/or to comply with study procedures
8. Symptomatic CNS metastases or carcinomatous meningitis. Asymptomatic patients must be clinically stable with regard to their CNS/meningeal metastatic involvement, have completed previous therapy (including radiation and / or surgery) at least 4 weeks prior to study drug administration, are not receiving steroid therapy or taper, and are not receiving anti-convulsive medication that were started for any CNS involvement
9. Active infection requiring IV antibiotics
10. Active autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of $\leq$ 10 mg/day prednisone
11. Sensory peripheral neuropathy $\geq$ Grade 2
12. Women of childbearing potential and men unwilling to practice an effective method of birth control from screening until 6 months after discontinuing study treatment. Childbearing potential is defined as sexually mature women who have not undergone a hysterectomy, have not been naturally post-menopausal for at least 23 consecutive months or have a serum FSH $<$ 40 mIU/mL. Effective methods of birth control are defined as surgical sterilization [e.g., bilateral tubal ligation, vasectomy], hormonal contraception [implantable, patch, oral], or double-barrier methods [any double combination of: intrauterine device, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap]), or abstinence from intercourse. Abstinence as a method of contraception is only acceptable as “true abstinence”, i.e. when it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
13. Significant cardiovascular or cerebrovascular disease within 6 months prior to Day 1 of Cycle 1, including any of the following:
    a) Prior history of hypertensive crisis or hypertensive encephalopathy
    b) TIA, PRIND or stroke
    c) History of acute coronary syndromes (including acute myocardial infarction, unstable angina, CABG, coronary angioplasty, or stenting)
    d) Aortic aneurysm requiring surgical repair
    e) Peripheral arterial thrombosis/thromboembolism
14. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
15. Current use of anticoagulants (e.g., warfarin or any other coumadin-derivate coagulants) at therapeutic doses within 7 days prior to study drug administration. Prophylactic use of unfractioned heparin or low molecular weight heparin (LMWH) is permitted (e.g., enoxaparin 40 mg QD)

16. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 **of Cycle 1**, or **abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to Day 1 of Cycle 1 or** anticipation of need for major surgical procedure during the course of the study or nonrecovery from side effects of any such procedure.
17. **History of intra-abdominal inflammatory process within 6 months prior to Day 1 of Cycle 1, including but not limited to peptic ulcer disease, diverticulitis, or colitis**
18. **Colonic prosthesis (stent) implant in place**
19. History of abdominal or tracheo-oesophageal fistula or GI perforation or intra-abdominal abscess within 6 months prior to Day 1 of Cycle1
20. **History of intestinal obstruction and/or c**linical signs or symptoms of GI obstruction **including sub-occlusive disease related to the underlying disease** or a requirement for routine parenteral hydration, parenteral nutrition, or tube feeding **within 6 months prior to Day 1 of Cycle 1. Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution**
21. **Chronic daily treatment with NSAID (occasional use for the symptomatic relief of medical conditions, e.g. headache or fever is allowed)**
22. **Chronic daily treatment with corticosteroids (dose > 10 mg/day methylprednisolone equivalent) excluding inhaled steroids**
23. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
24. Metastatic disease that involve major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume
25. History of broncho-pulmonary hemorrhage NCI CTCAE ≥ Grade 2 or gross hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to randomization
26. Severe, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture
27. Known dihydropyrimidine dehydrogenase deficiency or thymidylate synthase gene polymorphism predisposing the patient for 5-FU toxicity
28. Any other condition, diseases, metabolic dysfunction (e.g., uncontrolled diabetes mellitus), active or uncontrolled infections/inflammation, physical examination finding, mental status or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates patients participation in the clinical study due to safety concerns, compliance with clinical study procedures or that may affect the interpretation of the results

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Part I

Part I of the study is open label. After written informed consent has been obtained, sites will initially contact the IxRS to record patient details and to have a screening number assigned to the patient. When the screening status of the patient is known, the information will be entered onto the IxRS and patients will then be assigned a patient number.

Part II

After written informed consent has been obtained, sites will initially contact the IxRS to record patient details and to have a screening number assigned to the patient. When the screening status of the patient is known, the information will be entered into the IxRS and patients will then receive a patient number and be assigned to one of the two treatment arms. The unblinded pharmacist will prepare the infusion bag for the patient and will make sure the clinic staff and patient remain blinded. Patients should receive their first dose of study treatment on the day of randomization, but no later than 3 days after randomization.

Patients will be randomized in a double-blinded fashion in a ratio of 1:1 to receive mFOLFOX-6 + RO5520985 (experimental arm) or mFOLFOX-6 + bevacizumab (control arm). Patients will prospectively be stratified by region (United States vs. RoW) and number of metastatic sites (1 vs. $>$ 1). These stratification factors were chosen because of their potential to affect efficacy and/or safety outcomes, thus minimizing differences in treatment arms due to sources other than study treatment.

Randomization will be based on a pre-specified randomization list and will be stratified as described above. Information on stratification factors will be required from the investigator at the time of contacting the IxRS for randomization. Detailed instructions regarding the IxRS will be provided to each study center. The randomization numbers are to be allocated according to the specification document agreed with the IxRS provider.

Definition of the Double Blind

For Part II of the study, with the exceptions described below and in the safety and efficacy IMC charters, the randomization list will not be available to the project team at Roche or to any personnel at the study centers. Access to potentially unblinding data (i.e., PK data) will be restricted as described below.

The randomization list will be made available to the qualified individual responsible for preparing the study drug, to the individual(s) responsible for PK and PD bioanalysis and to statisticians or programmers at Roche/CRO who will provide the selected efficacy aggregate data to support the interim futility and administrative analysis as described in Section 6.10. The appropriate randomization list release form shall be used.

PK/PD data can be received and cleaned on an ongoing basis by the CRO responsible. They will handle and clean the data in a secure area which is not accessible by any other SMT member with the exception of the SPA and the statistician on the study.

In addition, a pharmacometrician may be unblinded to enable the frontloading of modeling activities. These activities are solely for building the pharmacometric models and frontloading the analyses. However, if presentation of such analyses to the project team is warranted for decision making during the study, data will only be presented cumulatively, to prevent unblinding of any given individual treatment assignment prior to database lock.

Emergency Unblinding

If unblinding is necessary for patient management (in the case of a serious adverse event), the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

As per health authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (Section 5.1) that are considered by the Investigator to be related to study drug.

In the event of an emergency, the treatment code for an individual patient will be readily available to the Investigator and Sponsor through the IxRS.

All such occurrences should be documented in the study file. Treatment codes should not be broken except in emergency situations and, if possible, the responsible scientific leader should be contacted before the code is broken.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding, at the investigational site end, will be documented in the study report with date, reason for identifying the drug and the name of all the person(s) who had to be unblinded.

Unblinding should not result in the withdrawal of the patients from the study. Every effort should be made to retain unblinded patients.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 RO5520985

The investigational medicinal product (IMP) for this study is RO5520985. It is provided as a sterile, colorless to slightly brownish liquid and contains no preservatives.

Each single-use, 10-mL vial contains 250 mg (nominal) of RO5520985 formulated as 25 mg/mL in L-histidine buffer solution (approximately pH 6.0) containing sucrose and polysorbate 20.

The recommended storage condition for RO5520985 drug product is between 2°C–8°C (36°F–46°F), protected from light. The nominal fill volume is 10 mL. A 0.2 μm in-line filter must be used for the administration. For batch-specific instructions and information on shelf-life see packaging. Study drug packaging will be overseen by the Sponsor's clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labeling of the study medication will be in accordance with Sponsor's standard and local regulations. The study drug must be stored according to the details on the product label. Upon arrival of investigational products at the site, site personnel should check the drug packaging for damage and verify proper identity, quantity, integrity of vials and seals and temperature conditions, and report any deviations or product complaints to the IxRS and monitor upon discovery. Any damaged shipments will be replaced.

For further details, refer to the RO5520985 IB.

4.4.1.2 Bevacizumab and FOLFOX

Bevacizumab and mFOLFOX-6 are considered to be standard of care and the comparator treatment ('Control Arm'). FOLFOX is a non-investigational medicinal product (non IMP) within this study. Being the comparator, bevacizumab is considered to be investigational medicinal product (IMP).

Bevacizumab

Bevacizumab will be provided by Roche. Study drug packaging will be overseen by the Sponsor's clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations. The study drug must be stored according to the details on the product label. Upon arrival, site pharmacy should check the drug packaging for damage and verify proper identity, quantity, integrity of vials and seals and temperature conditions, and report any deviations or product complaints to the IxRS and monitor upon discovery. Any damaged shipments will be replaced.

For further information including storage details, refer to Avastin® full prescribing information.

FOLFOX

The mFOLFOX-6 regimen contains 5-FU, folinic acid and oxaliplatin. It will be prescribed, sourced and funded according to local standard practice. For additional information including storage details, refer to the respective full prescribing information.

4.4.2 Dosage, Administration, and Compliance

The qualified individual responsible at the pharmacy for dispensing the study drug will prepare the assigned dose. This individual will write the date dispensed and patient number and initials on the study drug vial label and on the Drug Accountability Record. This individual will also record the study drug batch or lot number received by each patient during the study.

4.4.2.1 RO5520985 (PART I)

At least 6 patients will receive a fixed dose of 2000 mg RO5520985 IV on Day 1 of each Cycle on a Q2W schedule. Based on the observed toxicity, dose reduction of RO5520985 may become necessary. Therefore the Safety IMC may decide to enroll additional 6-12 patients which will be then treated at lower dose(s).

4.4.2.2 RO5520985 and Bevacizumab (PART II)

Dose of RO5520985 / bevacizumab

a) RO5520985

Patients randomized to the experimental arm will receive the fixed dose of RO5520985 IV on Day 1 of each Cycle on a Q2W schedule as recommended by the IMC based on Part I safety data review.

b) Bevacizumab

Patients randomized to the control arm will receive bevacizumab at a dose of 5 mg/kg IV on Day 1 of each Cycle on a Q2W schedule. Bevacizumab will be dosed by body weight. The weight at screening will be used for dose calculation for each patient. Recalculation of dosage is not required if weight changes.

Please note: Detailed information about the preparation of infusion solution of RO5520985 and including information about compatible infusion bags, administration sets and in line filters will be provided to the unblinded pharmacy in a separate pharmacy manual and in the Avastin® prescribing information, respectively

Administration of RO5520985/bevacizumab

The patients will receive either RO5520985 plus mFOLFOX-6 (experimental arm) or bevacizumab plus mFOLFOX-6 (control arm) every 2 weeks as described below. The first dose of RO5520985/ bevacizumab defines Day 1 of the treatment cycle. The last day of a complete treatment cycle is Day 14. RO5520985/ bevacizumab will be administered as an intravenous infusion only at room temperature through a dedicated line with a 0.2 μm in line filter and recommended product contact surfaces. IV infusion pumps should be used to control the infusion rate. RO5520985/ bevacizumab will be given without any routine premedication and prior to mFOLFOX-6.

RO5520985/ bevacizumab must be administered in a hospital or clinic equipped for intravenous chemotherapy. Full emergency resuscitation facilities should be

immediately available and patients should be under close supervision of the Investigator at all times.

RO5520985/ bevacizumab will be given over 90 minutes. Do not administer as an IV push or bolus. If the first infusion is tolerated without signs and symptoms of infusion–related reactions (IRR) CTCAE ≥ Grade 2, the second infusion will be administered over 60 minutes. All subsequent infusions may be given over 30 minutes, if infusion over 60 minutes is tolerated without an IRR CTCAE ≥ Grade 2.

For further details regarding administration of RO5520985 and bevacizumab refer to the RO5520985 pharmacy manual and full prescribing information of Avastin®, respectively.

4.4.2.3 FOLFOX

All patients of Part I and II regardless of the treatment arm will receive mFOLFOX-6 every 2 weeks as described below.

Please note: Chemotherapy infusion can start only after RO5520985/bevacizumab infusion has been completed and patient tolerability was checked. If an AE has been experienced during RO5520985/bevacizumab infusion, chemotherapy may be delayed up to a maximum of 24 hours.

- Oxaliplatin at a dose of 85 mg/m^2 IV over 120 (±5) minutes on Day 1 of each cycle
- Folinic acid at a dose of 400 mg/m^2, IV over 120 (±15) minutes on Day 1 of each Cycle. As an alternative levofolinic acid at a dose of 200 mg/m^2, IV over 120 (±15) minutes on Day 1 of each cycle can be given.
- 5-fluorouracil (5-FU) starting bolus on Day 1 of each Cycle at a dose of 400 mg/m^2 followed by 2400 mg/m^2 IV permanent infusion for 46 (±2) hours.

Oxaliplatin will be given concurrently together with folinic acid via a Y-connector. Thereafter 5-FU will be administered as described above.

During induction phase substitution of 5-FU/folinic acid is not permitted. During the maintenance phase substitution of 5-FU/folinic acid IV by oral capecitabine is discouraged. However, individual patients may receive capecitabine without folinic acid according to institutional standards (e.g., 625 mg/m^2 bid continuously (Koopman et al. 2013) at the discretion of the Investigator and in agreement with the Sponsor's medical monitor.

The preferred order and rate of drug administration may be modified based on patient tolerability or institutional guidelines. In the event that the full dose of folinic acid (racemic leucovorin or levoleucovorin) is unavailable and in accordance with NCCN guidelines, the dose may be lowered in accordance with the treating physician's standard practice in administering mFOLFOX-6. In case neither racemic leucovorin nor levoleucovorin is available, dose can be omitted and patients who tolerate treatment

without Grade 2 or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) can be considered. However, standard dosing should be resumed when supply is adequate.

For further details of preparation and administration, refer to the pharmacy manual, and full prescribing information for the individual components of FOLFOX.

4.4.2.4 Treatment Duration

Oxaliplatin will be administered for a maximum of 8 cycles as part of the induction therapy. Thereafter oxaliplatin administration will be discontinued and the patients receive maintenance therapy containing 5-FU/folinic acid plus either bevacizumab (control arm) or RO5520985 (experimental arm) for 24 months if treatment is not stopped earlier due to progressive disease, unacceptable toxicity, Investigator decision or consent withdrawal.

If a patient stops chemotherapy either in part or in whole, then they should continue on RO5520985 or bevacizumab for a maximum of 24 months (calculated from start of maintenance therapy) if treatment is not stopped earlier due to progressive disease, unacceptable toxicity, Investigator decision or consent withdrawal.

4.4.3 Accountability of RO5520985 and Bevacizumab

RO5520985 and bevacizumab will be provided by the Sponsor. The investigational site will acknowledge receipt, confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was dispensed
- All records and drug supplies must be available for inspection by the Roche/CRO Monitor at every monitoring visit

RO5520985 and bevacizumab will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed. Written authorization must be obtained from the sponsor at study start up before destruction.

The site must obtain written authorization from the Sponsor before any RO5520985 or bevacizumab is destroyed, and destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity [batch numbers, Patient Numbers] of product(s) destroyed
- Quantity of product(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person or company who destroyed products

Accurate records of RO5520985 and bevacizumab received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over–the–counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient 4 weeks prior to starting study treatment until End of Study visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All therapy and/or medication administered to manage adverse events should be recorded on the adverse event eCRF.

4.5.1 Permitted Therapy

Patients should be treated for all concomitant medical conditions and adverse events according to accepted standards of medical care at the discretion of the Investigator except as specifically prohibited in Section 4.5.2.

All patients are to receive standard supportive care, including blood and platelet transfusions, antibiotics, and anti-emetics, as appropriate. Colony-stimulating factors, such as G-CSF and erythropoietin, should be used according to local practice/institutional guidelines or the ASCO and ASCO/ASH guidelines, respectively (Smith et al. 2006; Rizzo et al. 2010).

On the basis of clinical experience with **RO5520985**, IRRs **are** classified as a potential risk of RO5520985 therapy **(Section 5.2.1.12)**. If IRRs occur, patients should be treated according to standard treatment of care. Further details with regard to management of IRRs are described in Section 5.2.3.2 (Table 2).

4.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and Clinical Pharmacologist/Clinical Scientist.

The following treatments are not permitted during the study:

- Any other investigational therapy
- Anticancer therapy (chemotherapy, hormonal, biological or radiation therapy, and surgery) other than study treatments
- Radiotherapy, except short course palliation

If any of these therapies are needed, the patient will be considered to have evidence of progressive neoplastic disease and have experienced treatment failure. This will lead to the patient discontinuing participation in the study.

Furthermore, due to the potential risk of bleeding associated with anti-angiogenic therapies, the following treatments are prohibited:

- Current use of full dose anticoagulants or thrombolytic therapy at therapeutic doses. **However, if a patient experiences a VTE event while still receiving study drug treatment, it may still be possible for him or her to remain on study medication. Please see Section 5.2.3.2 (Table 2) for guidance on further treatment with or discontinuation of bevacizumab/ RO5520985 therapy.**
- Prophylactic use of low dose anticoagulation, unfractionated heparin or LMWH is permitted. However, the preferred choice for anticoagulation treatment should be LMWH as per ASCO guidelines (Lyman et al. 2007). The prophylactic use of warfarin or coumarin-like products is not permitted.
- Prophylactic use of anticoagulation at baseline and during study treatment for the maintenance of patency of permanent indwelling central venous access devices is permitted. If a patient suffers a VTE event, while on study still receiving study treatment, it may still be possible for him or her to remain on study treatment (Section 5.2.3).

In addition, due to the potential risk of severe/fatal infections in patients treated with 5-FU, the following treatment is prohibited:

- Vaccination with live vaccines

Also prophylactic use of phenytoin is not allowed in combination with 5-FU.

Concomitant **chronic** use of NSAIDs while receiving study drugs is **prohibited**. **However, for the symptomatic relief of medical conditions** (**e.g. headache, fever) sporadic or short-term intake of oral NSAIDs is allowed, when co-administered proton pump inhibitors to reduce potential gastrointestinal damage. Also** seek consultation with a gastroenterologist as medically indicated.

Chronic daily treatment with systemic corticosteroids (dose >10 mg/day methylprednisolone equivalent) is generally prohibited while on RO5520985/ bevacizumab. However, a one-time or medically indicated, short course of higher

dose (>10 mg/day methylprednisolone equivalent) of systemic corticosteroid use may be allowed as agreed by the study investigator and the Medical Monitor.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the SoA (Appendix 1, Appendix 2, Appendix 3) for both Part I and Part II of the study, except soluble biomarker assessments in Part I and FOLFOX PK in Part II. These tables provide the minimum requirements for the protocol. Additional assessments and/or additional parameters may be performed as clinically indicated, according to Investigator judgment.

4.6.1.1 Medical History and Demographic Data

Medical history will be taken that describes clinically significant diseases within the previous 5 years apart from cancer. Demographic data to be collected will include date of birth and sex. Additionally, anthropometric measurements will include race, body weight (at physical examinations) and body height (body height to be measured during screening only). To explore any potential influence of race on PK and PD, information on race will be collected in the eCRF.

4.6.1.2 Cancer History

Cancer history will also be collected including cancer type, cancer location, histology date and stage of first diagnosis, tumor stage at study entry, prior anticancer treatment, surgery and radiotherapy.

4.6.1.3 Physical Examinations

Physical examinations will occur throughout the study according to the Schedule of Assessments (Appendix 1). A complete physical examination should include an evaluation of the head, eyes, ears, nose and throat. The cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurological systems should also be examined. Any abnormality identified at baseline should be recorded on the Medical History eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.1.4 ECOG Performance Status

Performance Status (PS) will be measured using the ECOG Performance Status Scale. PS will be assessed with each physical exam. It is recommended, where possible, that a patient's PS will be assessed by the same person throughout the study.

4.6.1.5 Vital Signs

Vital signs will include measurements of blood pressure, respiratory rate, body temperature, and pulse rate (in sitting position upon resting for 5 minutes). Medically significant findings that are present prior to the start of study treatment must be recorded in the Medical History eCRF with “ongoing” ticked. Medically significant findings made after start of study treatment or worsening of those reported at baseline and which meet the definition of an AE (Section 5.3.5.5) must be recorded as an AE in the eCRF.

4.6.1.6 Electrocardiograms

A 12-lead ECG will be performed and should be obtained for each patient from the same machine whenever possible as indicated in the SoA (Appendix 1) or as clinically indicated. Triplicate ECG recordings will be obtained within approximately 2–5 minutes of each other. The average of the three readings will be used to determine ECG intervals (e.g., PR, QT).

ECG characteristics, including heart rate, QRS duration, PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction) and QTcF (Fridericia's correction) and RR will be calculated within eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation by the Investigator or another qualified assessor will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

The diagnostic comments on the ECG machine printout will not be captured. Significant findings must be recorded either as Relevant Medical History/Current Medical Conditions (if present before treatment) or as Adverse Events (if newly occurring or worsening since starting treatment). The Investigator or designee must review, sign and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site as well. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each patient. The conditions should be as close as possible to pre-dose time points; this includes but is not limited to food intake, activity level, stressors and room temperature.

4.6.1.7 Transthoracic Echocardiogram/Multiple Gated Acquisition Scans

TTE (transthoracic echocardiogram) or MUGA (multiple gated acquisition) scan will be performed according to the standard practice of the investigational site. This may be further repeated at the Investigator’s discretion if there are signs or symptoms of cardiotoxicity. TTE or MUGA scan will be used to monitor the cardiac parameters of function (i.e., left ventricular ejection fraction [LVEF]). The same method should be applied for an individual patient throughout the study. Preferably the same cardiologist

should read and report the outcome to minimize variability in results. Copies of all echocardiograms/scans performed on patients who experience a ≥ 20% decrease in LVEF from baseline and whose cardiac ejection fraction is below the institution's lower limit of normal may additionally be required by the Sponsor for review and thus be kept as part of the patient's permanent study file at the site.

4.6.1.8 Adverse events

Adverse events will be graded according to the NCI Common Terminology Criteria (NCI–CTCAE) version 4.03.

4.6.1.9 Concomitant Medication

Refer to Section 4.5 for details on concomitant medication.

4.6.1.10 Safety Laboratory Assessments

The following safety laboratory assessments will be performed according to the SoA (Appendix 1):

- Hematology: Hemoglobin, hematocrit, platelet count, RBC count (erythrocytes), WBC count (leukocytes), WBC absolute differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes).
- Serum chemistry: Na, K, Ca, lipase, glucose, GGT, AST, ALT, LDH, AP, total and direct bilirubin, urea, creatinine, total protein, albumin, CK, TSH, CRP and CrCl calculated (by Cockroft-Gault formula) or directly measured.
- Coagulation: INR/PT; aPTT, fibrinogen
- Blood tumor marker: CEA
- Urine analysis: Urine dipstick for proteinuria (24-hrs urine protein analysis in 2+ or greater urine dipstick reading).
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum or urine pregnancy test at Screening. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

All samples for safety laboratory assessments will be sent to the study site's local laboratory for analysis. Normal ranges for the study laboratory parameters must be supplied to the CRO before the study starts. The total amount of blood drawn for all above described safety parameters will be approximately 12 mL during screening and approximately 12 mL for each subsequent safety laboratory assessment.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse (e.g., previous occasional intake of a medication or

food containing for example codeine, benzodiazepines or opiates) the test could be repeated to confirm washout.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local laboratory.

4.6.1.11 Pharmacokinetic Assessments

Part I of the study

PK samples for RO5520985 and FOLFOX will be collected as outlined in the SoA (Appendix 2, Appendix 3). For each scheduled time point of RO5520985 and 5-FU, an approximate venous blood volume of 2 mL for each compound will be drawn. For each scheduled time point of oxaliplatin (free and total), an approximate venous blood volume of 4 mL will be drawn. In Part I, the total amount of blood drawn for PK (including HAHA) is approximately 149 mL.

Part II of the study

Samples for RO5520985 PK analysis will be collected as outlined in the SoA (Appendix 2). Samples from patients receiving bevacizumab will be taken as per the RO5520985 schedule to maintain the double-blind design of the study, but will not be analyzed. PK parameters of FOLFOX will not be measured in Part II of the study. At each scheduled timepoint approximately 2 mL of venous blood for plasma isolation will be drawn. In Part II, the total amount of blood drawn for PK (including HAHA) is approximately 70 mL.

General Instructions For PK Sampling (applies to Part I and Part II)

All blood samples for PK assessment will be collected from an alternative IV line which should be on the opposite arm to that used for administering the infusion.

The date and time of each PK sample will be recorded. Additional unscheduled PK samples will be collected for RO5520985 at time of disease progression or at earliest convenience thereafter.

For each unscheduled PK sample, it is essential to capture on the eCRF the date and time of the event necessitating the unscheduled sample (PD) and of the last dose preceding the unscheduled sample.

Instruction manuals and supply kits will be provided for all PK assessments. For collection procedures, storage conditions and shipment instruction, refer to Sample Handling and Logistics Manual.

4.6.1.12 Human Anti-Human Antibodies

Sampling will be conducted to determine if HAHAs are developed against RO5520985. Samples from patients receiving bevacizumab will be taken as per the RO5520985 schedule to maintain the double-blind in the study, but will not be analyzed. In first instance only HAHA samples collected at baseline and EoS Visit from patients treated with RO5520985 wll be analyzed. Only in case of positive HAHA titers (in one or both samples) or in case of IRRs, the remaining collected blood samples will be analyzed. For analysis purposes approximately 2 mL of venous blood for plasma isolation will be drawn.

Samples will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided and collection procedures, storage conditions and shipment instructions are detailed within the Sample Handling and Logistics Manual.

4.6.1.13 Pharmacodynamics and Exploratory Biomarker Assessments

The following samples will be collected for exploratory analyses:

- Plasma
- Archival primary tumor tissue

Note: Soluble biomarkers (plasma) will not be measured in Part I patients.

The rationale for their collection is provided in Section 3.2.4. Additional markers may be measured if a strong scientific rationale for these analyses develops. All data arising from the samples will be subject to the confidentiality standards described in Section 8.4. The collection time points are specified in the SoA (Appendix 1).

Note: Samples at Disease Progression visit should be drawn within 1 week after imaging shows Disease Progression. In the event that the EoS Visit overlaps with Disease Progression Visit, only 1 sample needs to be drawn.

On the basis of continuous analysis of the data in this study and other studies, any sample type may be stopped at any time if the data from the samples collected does not produce useful information.

For collection procedures, storage conditions and shipment instructions see the SampleHandling and Logistics Manual.

4.6.1.13.1 Plasma

Approximately 7.5 mL blood sample for plasma isolation will be obtained for each timepoint (Appendix 1). The plasma will be used for the following assessments:

- Levels of circulating targets: Ang-2 and VEGF-A

- Angiogenesis-related markers (but not limited to): Ang1, PlGF, sTie-2, VEGF-C, sVEGF-R1, sVEGF-R2, sVEGF-R3, SDF-1α, E-selectin, ICAM-1, bFGF, IL-8, PDGF-C, CA-IX

Blood (2 mL) for plasma isolation will be obtained at baseline, disease progession as well as end of study visit and used to measure levels of circulating MMP-2 and MMP-9.

An additional approximate 2 mL blood sample will be collected at baseline for development of an Ang-2 companion diagnostic test, as well as a total of approximately 6 mL blood for 3 additional measurements of Ang-2 (Appendix 2).

In addition 10 mL blood sample for plasma isolation will be required for the following assessment:

- Dependent on the mutational analysis of the archival tissue (Section 4.6.1.13.2) based on the specific mutation detected, the presence of circulating tumor DNA (ctDNA) will be assessed at baseline and various time points on treatment (SoA, Appendix 1).

Total Blood Loss

The total blood volume loss for plasma and whole blood biomarker assessments will be approximately 140 mL up to Cycle 13 including the Disease Progression and End of Study Visit.

Residual plasma samples will be retained for 15 years to enable validation of companion diagnostic tests related to the proposed mechanism of action of the active principle RO5520985 from all patients enrolled on the study. Any residual PD samples not to be used for the validation mentioned above will be destroyed 2 years after the date of final closure of the clinical database.

4.6.1.13.2 Archival Primary Tumor Tissue

Representative tumor specimens in formalin-fixed, paraffin embedded blocks (preferred) or slides (35 slides if possible) with an associated pathology report are to be obtained from all patients at all sites. Tumor blocks/slides must be sent as indicated in the lab manual for central extended RAS mutational analysis.

In cases where local RAS mutational analysis is available prior to study entry, this information will be shared with the Sponsor and collected within eCRF.

In addition tumor tissue will be analyzed to assess further potential response prediction marker. This includes the analysis of (but is not limited to):

- Target proteins and biomarkers related to their vascular signaling including Ang-2, VEGF-A, Ang-1, Tie-2
- Markers of vessel architecture by IHC including CD31, CD34, Podoplanin, aSMA, c-C3, Ki67. The analysis will be prioritized based on the amount of material available. Additional assessments may be performed.

- Markers characterizing the tumor status including Ki67and CAIX. The analysis will be prioritized based on the amount of material available. Additional assessments may be performed.
- Markers of tumor-infiltrating immune cells including CD4, CD8, CD3/FOXP3, CD68/CD163,CD3/perforin. The analysis will be prioritized based on the assay and material availability. Additional assessments may be performed.
- Molecular mutational analysis including, but not limited to mutational status of e.g. EGFR, BRAF

Tumor blocks will be returned to sites latest at study end. If there is urgent need for the block to be returned and this is requested by the Investigator, the blocks will be sent back within approximately 2 weeks upon notice. On the chance that further analyses are required, access to the block from the site will be requested again, in the event that it was returned already. Slides will not be returned to the sites.

Further exploratory analyses, which could lead to hypothesis generation for potential response prediction markers, will be performed. This includes, but is not limited to, gene expression profiling (e.g., with RNA sequencing technology).

The remaining tissue/slides will be stored in the RCR for 15 years for all consenting patients.

4.6.1.14 Disease-Specific Assessments
Tumor and Response Evaluations

Throughout the trial, the RECIST criteria, v. 1.1 (Appendix 8) will be applied when assessing any responses to the study drug treatment. All potential sites of tumor lesions will be assessed at baseline by radiologic techniques using contrast enhanced CT or MRI imaging. All tumor lesions at baseline need to be recorded as either target or nontarget lesions.

The minimum schedule of imaging is the thorax, abdomen, and pelvis. If there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule, further investigations should be performed with a view to documenting the full extent of the tumor burden at baseline according to the investigator's clinical judgment. Results of tumor assessments using CT/MRI performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; in this case no further CT/MRI is required during screening. Subsequent scans are done every 8 weeks ($\pm$ 7 days) thereafter and at End of Study Visit. All complete and partial responses must be confirmed by a second assessment at least 4 weeks later. In the event of SD, follow-up assessments must have met the RECIST v1.1 SD criteria at least once after study entry at a minimum interval of 8 weeks.

Should a patient discontinue from treatment for any reason other than progression, an End of Study CT/MRI is to be performed only if it has not been done $\leq$ 28 days prior. **Patients who discontinued the study for any other reasons than progression will**

be followed by regular CT assessments according to institutional standard of care until documentation of progressive disease, initiation of another anticancer therapy (including secondary resection), withdrawal of consent, or death.

Patients with previously documented tumor progression will not require additional tumor reassessment by CT/MRI at End of Study visit.

If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment.

Patients with target lesions that have become centrally necrotic and meet the RECIST criteria of progressive disease, but otherwise demonstrate clinical symptoms improvement and tumor marker decrement, may remain on study treatment upon decision of the Investigator and the Sponsor's medical monitor.

If study drug treatment is delayed for any reason, the scheduled tumor assessments should still take place within the scheduled assessment window.

Consistency of consecutive CT or MRI scans should be ensured during all assessments for each patient, with the same technique used for evaluating lesions throughout the treatment period. Use of spiral CT or MRI is required for baseline lesions $<$20 mm and must be documented in medical records and used consistently throughout the study. If more than one method is used, select the most accurate method according to RECIST v1.1 when recording data. Other methods (X-ray, ultrasound, etc.) are not acceptable for monitoring target lesions. The use of oral and IV contrast should be used consistently where no contraindication exists and where appropriate. An adequate amount of contrast agent should be given, so that the tumor lesions appear with good resolution. If possible, a single radiologist should perform all evaluations for an individual patient.

Note: Any lesions that have been previously treated with radiotherapy should not be used as target lesions for tumor assessment. Exceptions may be made when these lesions are the only lesions available for evaluation and have shown definite progression since their last radiation treatment.

4.6.1.15 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and

analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Rationale

The pharmacogenetic information gathered through the analysis of specimens in the RCR should improve treatment outcome by predicting which patients are more likely to respond to specific drug therapies, predicting which patients are susceptible to developing adverse side effects and/or predicting which patients are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable DNA variations will be double coded: a new independent code will be added to the first code to increase confidentiality and data protection (Section 8.4). The results of specimen analysis from the RCR will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

All RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will also be made available for future biomarker research towards further understanding of RO5520985 treatment of CRC, related diseases and adverse events and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the Roche Clinical Repository policy to ensure the appropriate use of the RCR specimens. If no consent has been given for long term storage, all samples will be

destroyed no later than 5 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.

Sample Collection

Specimens for dynamic (noninherited: plasma), genetic (inherited: DNA), and tissue biomarker discovery and validation will be collected from all consenting patients participating in the trial. Tissue slides and plasma samples will be single coded like any other clinical sample (labeled and tracked using the patient's study identification number), DNA samples will be double-coded (refer below to paragraph "Confidentiality" for more details).

Note: No blood samples will be collected for RCR in Part 1

Blood for Plasma

Blood (one sample with approximately 6 mL in a tube with EDTA) for plasma isolation will be collected at baseline for biomarker discovery and validation, which may include analysis of proteins and metabolites and other candidate advanced biomarkers.

Blood Sample for Genetic Analysis

Blood (approximately 6 mL in K3 EDTA) for DNA isolation (e.g., genome-wide association studies) will be collected as at baseline. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. The sample may be tested using a variety of methodologies including but not limited to DNA sequencing. The biological specimen collection will be used to understand better protocol treatment effect, adverse effects and related disorders. Since the identification of new markers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of analysis remains to be determined.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality for Genetic Biomarker Specimens

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure study subject confidentiality for RCR specimens and associated data. Upon

receipt by the RCR, each specimen is "double-coded" by replacing the study subject identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the study subject identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The Investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient’s agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BP29262 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BP29262.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study–specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

An ESF documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pretreatment assessments will be performed within 28 days prior to Day 1, unless otherwise specified. In cases with an unexpected delay due to logistical or technical reasons, the screening period can be extended. Extending the screening period beyond 28 days requires Sponsor approval. The approval of extended screening will be handled via IxRS.

4.6.2.2 Assessments during Treatment

Under no circumstances will patients who enroll in this study and have completed treatment as specified, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoA (Appendix 1, Appendix 2, Appendix 3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoA.

All assessments must be performed on the day of the specified visit, unless a time window is specified in the SoA.

4.6.2.3 Assessments at End of Study Visit

If, for any reason, study drug treatment is permanently discontinued, the patient will be considered to have completed study drug treatment. Patients who discontinue study drug treatment should be scheduled for an End of Study Visit within **5 (±1) weeks** after discontinuing study drug treatment, at which time all of the assessments listed in the SoA (Appendix 1) for the End of Study Visit will be performed.

4.6.2.4 Follow-Up Assessments

All patients will be followed for subsequent anticancer therapy and survival (e.g., by phone call) approximately every 3 months after EoS Visit until death, loss to follow-up, or study termination by Roche, whichever occurs first. **Anticancer therapy is collected at first FU visit and is only collected at the subsequent FU visits if the therapy is different from previous one**. In addition there will be one optional post study assessment for determination of HAHA (Appendix 1).

After the EoS Visit, adverse events should be followed as outlined in Sections 5.4 and 5.5.

4.6.2.5 Assessments at Unscheduled Visits

See Appendix 1 for assessments that are required to be performed in case of an unscheduled visit.

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from study drug treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

- Unacceptable toxicity
- Investigator or Sponsor determines it is in the best interest of the patient
- Disease progression
- Patient noncompliance to the study and/or study procedures

4.7.1.1 Discontinuation from Study Drug

Adverse events requiring discontinuation from study drug are described in Section 5.2.3.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a **End of Study** Visit (Section 4.6.2.3) and may undergo follow-up assessments (Section 4.6.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. In Part I of the study, patients who discontinued study drug during the first two cycles not for safety reasons may be replaced at Sponsor discretion. In Part II of the study, patients who discontinue study drug prematurely will not be replaced.

If a patient discontinues therapy for reasons other than progression, the patient will be followed by regular CT assessments **according to institutionalstandard of care** until documentation of progressive disease, initiation of another anticancer therapy (**including secondary resection)**, withdrawal of consent, or death.

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients will not be followed for any reason after consent has been withdrawn.

Note: Patients withdrawing from the main study have the possibility to provide consent to continue in the follow-up phase for collection of further information on disease and survival follow-up (Appendix 1 of main ICF).

In Part I patients who discontinued study drug during the first two cycles not for safety reasons may be replaced at Sponsor discretion. Patients who withdraw from Part II the study will not be replaced.

4.7.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Unfavorable benefit/ risk- assessment based on interim analysis
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

In terminating the study, the Sponsor and the Investigators will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/EC and Regulatory Agencies will be informed accordingly.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and nonserious adverse events of special interest; measurement of protocol–specified safety laboratory assessments; measurement of protocol–specified vital signs, ECGs; and other protocol–specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.1.2.

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X–ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death).

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (e.g. NCI CTCAE criteria; Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.3.7 for reporting instructions).

5.1.3 Selected Adverse Events

The incidence of the following selected adverse events (grades according to NCI CTCAE v4.03) will be collected:

- Hypertension (Grade ≥ 3)

- Proteinuria (Grade ≥3)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events (Grade ≥3)
- Vascular disorder - other: Thrombotic microangiopathy (any grade)
- Gastrointestinal perforation (any grade)
- Fistula involving an internal organ (any grade)
- Fistulae (Grade 4)
- Wound healing complication (Grade ≥3)
- Bleeding/hemorrhage (Grade ≥3)
- Pulmonary bleeding (Grade ≥2)
- CNS bleeding (Grade ≥2)
- Congestive heart failure (Grade ≥3)
- Reversible posterior leukoencephalopathy syndrome (any grade)

5.1.4 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.7 for reporting instructions). Adverse events of special interest for this study include the following:

- **Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.**
- **Suspected transmission of an infectious agent by the study drug, as defined below:**

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2 SAFETY PLAN

5.2.1 Risks for RO5520985 (Vanucizumab) and Bevacizumab

Information in the following sections is based on the mechanism of action, preclinical and clinical data for RO5520985 and bevacizumab. For further information, refer to the RO5520985 (vanucizumab) IB and, the bevacizumab (Avastin) prescribing information.

5.2.1.1 Gastrointestinal Perforation

In patients treated with bevacizumab, the incidence of gastrointestinal perforation ranged from 0.3 to 3.2% across clinical studies. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2% - 1% of all bevacizumab treated patients.The majority of cases occurred within the first 50 days of initiation of bevacizumab.

In Study BP28179, 6 events indicative of gastrointestinal perforation were reported in 6/115 (5.2%) patients; two of the events had a fatal outcome. In Part II, a [redacted]-year old [redacted] with metastatic adenocarcinoma of the pancreas developed Grade 4 gastrointestinal perforation (related). In Part III, 5/41 (12.2%) patients with platinum resistant ovarian cancer developed GI-perforation, two of the events had a fatal outcome.

In the blinded Part 2 of Study BP29262 (vanucizumab or bevacizumab plus mFOLFOX-6 in metastatic colorectal cancer), the incidence of GIP events (including perforation, intra-abdominal abscess, and GI fistula) was 11.1% (8/72 patients) in Arm A versus 5.6% (4/71 patients) in Arm B. One/12 patients with GI-perforation had a fatal outcome.

5.2.1.2 Fistula (other than GI)

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1–10% incidence) in patients with mCRC, but uncommon (0.1–1%) or rare (0.01–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

In clinical trials with RO5520985, 2 events of fistula formation have been reported in 2/123 patients (1.6%) treated with RO5520985, both in Study BP28179: one patient with rectal cancer and previous radiotherapy experienced a Grade 3 vesico-cutaneous fistula, which resolved with conservative management following discontinuation of RO5520985 treatment, and a Grade 2 cutaneous fistula was reported in one patient with an oral adenoid-cystic carcinoma.

5.2.1.3 Hemorrhage

Risks of hemorrhage, especially tumor-associated hemorrhage, are substantial among angiogenesis inhibitors. Patients with different types of cancer vary in their risk of hemorrhage due to the anatomic location of the tumor, its underlying biology, or its associated treatment. Pulmonary hemorrhage is a rare but serious potential adverse effect that may occur during treatment with anti-VEGF agents.

In particular, patients who have squamous non small cell lung cancer are at an increased risk of pulmonary hemorrhage owing to the underlying disease process. Severe pulmonary hemorrhage is a medical emergency requiring specialized management and patients with massive bleeding should be cared for in the intensive care unit.

Treatment with bevacizumab can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2 to 4.6%. Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving bevacizumab and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone. In clinical studies in non -small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of bevacizumab were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 bevacizumab-treated patients (rate 1.2%, 95% CI 0.06%-5.93%). Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3-4 hemorrhage.

In clinical trials with RO5520985, 27 AEs suggestive of hemorrhage have been reported in 21/123 patients (17%). In Study BP28179, 1 patient experienced a Grade 2 cerebral (subarachnoidal) hemorrhage. Three events of hemoptysis were reported: 1 patient with a large centrally located mediastinal mass experienced hemoptysis (pulmonary hemorrhage) with a fatal outcome; the other 2 events of hemoptysis reported in 2 patients were of Grade 1 intensity. The remaining events of epistaxis, hematuria, gingival bleeding, eye hemorrhage, mouth hemorrhage, melena, blood urine present, vaginal hemorrhage, contusion and purpura were all of Grade 1 or 2 intensity. In Study BP29262 (safety run-in), 3 patients experienced 5 events suggestive of bleeding/hemorrhage: Grade 1 rectal hemorrhage, Grade 1 epistaxis and gingival bleeding, Grade 1 epistaxis and Grade 2 hemorrhoidal hemorrhage.

5.2.1.4 Arterial Hypertension

It has been demonstrated in animal models that VEGF induces endothelium-dependent coronary artery relaxation. In animals and man, VEGF preferentially dilates small arterioles and venules, and by doing so it induces a decrease in blood pressure. VEGF induces the phosphorylation of endothelial nitric oxide synthase resulting in an increased production of endothelial type nitric oxide,

which directly acts on endothelium. Considering this vasodilative effect of VEGF, it can be understood that functional blockade will induce vasoconstriction and hypertension. Hypertension in response to angiogenesis inhibitors might not only be induced by the lack of vasodilatory effects, but may also be due to a decrease in the number of small arteries and arterioles as a consequence of inhibiting new vessel formation. Effects of VEGF inhibition on the control of blood pressure by the kidney may also be involved after prolonged treatment.

An increased incidence of arterial hypertension (all grades) has been observed in patients treated with bevacizumab. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

In clinical trials with RO5520985, arterial hypertension was the most common adverse event and was reported in 73/123 (59.3%) patients. In Study BP28179, 68/115 (59.1%) patients reported events of arterial hypertension. In 29 patients arterial hypertension was of Grade 3 and in 2 patients of Grade 4; all but one of these AEs were considered to be related to study treatment. There has been one SAE of Grade 4 hypertensive encephalopathy and one SAE of G4 hypertension.

In the safety run-in of Study BP29262, arterial hypertension was reported in 5/8 patients. Grade 3 arterial hypertension occurred in 3 patients with pre-existing hypertension. There were no patients with hypertension Grade ≥ 4. Arterial hypertension was transient and adequately controlled by standard oral anti-hypertensive medication, not requiring discontinuation or reduction in dose of the study drug.

5.2.1.5 Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is a disorder characterized by microvascular thrombosis with thrombocytopenia, hemolytic anemia and red blood cell fragmentation. It is most commonly separated into two disorders: hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura. HUS refers to the triad of renal failure, thrombocytopenia and microangiopathic hemolytic anemia, which is usually demonstrated by red cell fragments and increased serum lactate dehydrogenase.

TMA is labelled for bevacizumab primarily as a renal disorder, which is typically manifested as proteinuria. Renal TMA has been reported in patients receiving bevacizumab but in the post- marketing setting only.

In clinical trials with RO5520985, thrombotic microangiopathy was reported in 2/123 patients (1.6%), both in Study BP28179: one Grade 3 SAE in Part I (30 mg/kg QW) which resulted in discontinuation of treatment with RO5520985and one non-serious event (Grade 1) in Part II: (30 mg/kg Q2W). Both events were assessed as related to RO5520985.

5.2.1.6 Venous Thromboembolic Events

An increased incidence of venous thromboembolic events has been observed in patients treated with bevacizumab. In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the bevacizumab containing arms compared to 3.2% to 15.6% in the chemotherapy control arms.

The underlying mechanism is unclear; however, dysfunctional or damaged endothelium is considered, whereas platelets as carriers of VEGF have also been suggested to play a role in the increased incidence of these events. Inhibition of VEGF-A prevents endothelial cell renewal in response to trauma, resulting in dysfunction of the endothelium and exposure of sub-endothelial collagen secondary to defects in the lining of the interior vasculature. The exposed sub-endothelium releases tissue factor, thereby activating the coagulation cascade. Although there are numerous mechanisms to control the coagulation cascade, the inhibition of VEGF-A eliminates a vital step in normal hemostasis and promotes thrombogenic activity. The risk of thrombosis with antiangiogenic therapy may be increased by the prothrombotic activity of tumor cells. Malignant cells promote thrombosis by a number of different mechanisms, including procoagulant activity, fibrinolytic activity, cytokine release, and direct interaction with endothelial cells, macrophages, and platelets.

In clinical trials with RO5520985, 6/123 patients (4.9%) experienced 6 venous thromboembolic events: In Study BP28179 2 SAEs of Grade 3 pulmonary embolism (not related), leading to withdrawal of RO5520985, a non-serious and related AE of Grade 2 deep vein thrombosis, one related non-serious AE of Grade 2 jugular vein thrombosis and one non-serious unrelated AE of Grade 1 superficial thrombophlebitis have been reported. During the safety run-in of Study BP29262, 1 patient had a non-serious and related AE of Grade 2 venous embolism.

5.2.1.7 Arterial Thromboembolic Events

An increased incidence of arterial thromboembolic events (e.g., new onset or worsening of unstable angina, myocardial infarction, transient ischemic attack) have been observed in patients treated with bevacizumab. Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATEs occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the bevacizumab containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving bevacizumab in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years.

In clinical trials with RO5520985, no arterial thromboembolic events have been reported.

5.2.1.8 Congestive Heart Failure

Congestive heart failure (CHF) is expected with bevacizumab. VEGF plays a critical role in coordinated tissue growth and angiogenesis in the heart. Blocking this pathway may interfere with cardiac remodeling and lead to heart failure. Increased peripheral resistance of the vasculature may be responsible for a reduced LVEF which may precede CHF.

Cardiovascular monitoring will be implemented for this study. Any patient who develops symptoms compatible with cardiovascular abnormalities should have prompt evaluation by a cardiologist.

In clinical trials with RO5520985, one SAE of congestive heart failure was reported (Study BP29262 safety run-in).

5.2.1.9 Proteinuria

An increased incidence of proteinuria has been observed in patients treated with RO5520985. The incidence and severity of proteinuria was increased in patients receiving bevacizumab as compared to controls. In a meta-analysis of seven trials with bevacizumab in mCRC the incidence of Grade ≥ 3 proteinuria was 1.7% (Hurwitz et al 2013). Possible mechanisms include: 1) Role of VEGF pathway in maintaining the integrity of the glomerular filtration barrier: VEGF is constitutively expressed by podocytes and VEGF receptors are present on normal glomerular capillary endothelial cells; 2) Thrombotic microangiopathy: glomerular capillary endothelial injury by this process can manifest as proteinuria and could represent one permutation of vascular thromboembolic disease seen with bevacizumab. This condition is diagnosed by renal biopsy and may not correlate with degree of proteinuria; and 3) Mediated through nitric oxide inhibition and associated with hypertension: in some patients, both hypertension and proteinuria uniformly decreased after cessation of anti-VEGF therapy suggesting a possible hemodynamic mechanism similar to the temporary proteinuria related to nitric oxide blockage inducing renal hemodynamic alteration occurring after exercise.

In Study BP28179, 12/115 patients (10.4%) experienced 20 events of proteinuria. All but 2 of these events were considered related to treatment with RO5520985. One patient had Grade 1 proteinuria (related) in the safety run-in of Study BP29262.

5.2.1.10 Wound Healing Complications

An increased incidence of wound healing complications, including serious and fatal complications have been observed in patients treated with bevacizumab. In a controlled clinical trial with bevacizumab in patients with mCRC who underwent surgery during the course of bevacizumab treatment, there was an increased

incidence of wound healing complications, including serious and fatal complications. In a meta-analysis of seven trials investigating mCRC, the incidence of Grade ≥ 3 wound healing adverse events was 0.9% (Hurwitz et al 2013).

In clinical trials with RO5520985, one event of Grade 1 wound complication assessed as related to treatment with RO5520985 has been reported (Study BP28179).

5.2.1.11 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a rare neurological syndrome which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Two confirmed cases (0.8%) of PRES have been reported in one clinical study with bevacizumab. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Although not fully understood, the mechanism of PRES is considered to be secondary to failed autoregulation of cerebral blood flow leading to cerebral vasogenic edema. Failed cerebral vascular autoregulation results in hyperperfusion and dilatation of cerebral arterioles, disruption of the endothelium, immediate breakdown of the blood-brain barrier, and finally, transduction of plasma and red blood cells into the interstitium. Although, inhibition of VEGF signaling is implicated in the pathophysiology of this syndrome, the syndrome often has other contributing factors and has not yet been replicated after VEGF inhibition in preclinical models.

In clinical trials with RO5520985, no events of PRES have been reported.

5.2.1.12 Infusion Related Reactions and Allergic Reactions

Allergic/anaphylactic reaction may occur following administration of proteins to patients (Lenz et al. 2007). Intravenous administration of therapeutic proteins can also be associated with infusion related reactions (IRR) which may be clinically indistinguishable from allergic/anaphylactic reactions. The infusion associated symptoms may accompany the first or subsequent drug administrations and may include skin rash, fever, chills, shortness of breath, hypotension, headache, nausea, and emesis. If severe, the symptoms of IRRs may be clinically indistinguishable from true anaphylactic reactions, which also may occur with the administration of proteins. Mediators classically associated with IRRs include TNF-α, IL-6, IL-8, and interferon (IFN)γ.

In clinical studies with bevacizumab, IRRs with the first dose of bevacizumab were uncommon. Bevacizumab-associated IRRs occurred at an incidence of less than 3% in a clinical trial setting; severe reactions were noted in 0.2% of patients. Therefore, premedications are not routinely administered with the use of bevacizumab.

In vitro cytokine release assay using blood from 28 healthy human donors suggested that there is no substantial risk for cytokine release or peripheral immune-cell depletion upon first infusion with vanucizumab.

In Study BP28179, 1 patient experienced Grade 2 IRR considered related to RO5520985. In addition, 36/115 patients (31.6%) reported events that occurred during RO5520985 infusion or within 24 hours after the end of infusion, were assessed as related to RO5520985 and after medical review might suggest signs and symptoms of IRR[1]: influenza-like illness, hypersensitivity, hypertension, chest pain, musculoskeletal pain, headache, abdominal pain, nausea, vomiting, asthenia, fatigue. In Study BP29262 (safety run-in), 1 patient experienced Grade 2 chills, suggestive of IRR.

Bevacizumab and RO5520985 are to be administered in a controlled setting with emergency equipment and staff who have been trained in the management of IRRs. Signs or symptoms of IRR may occur during or shortly after infusion. If IRR occur, the infusion of RO5520985/bevacizumab should be temporarily slowed down or interrupted until resolution of symptoms and general standard of care should be applied. Patients will be monitored until complete resolution of symptoms and treated as clinically indicated.

5.2.1.13 Immunogenicity

RO5520985 is a recombinant bi-specific mAb with IgG-like properties, and as with mAb-based therapies, there exists a potential for development of human anti-human antibodies (HAHAs) after treatment with RO5520985. The immunogenicity risk for RO5520985 will be assessed through plasma samples for detection of HAHA at baseline and during and after study treatment and in the event of a hypersensitivity reaction CTCAE ≥Grade 3.

For bevacizumab, post baseline HAHAs could be detected in less than 1% of patients not associated with allergic/hypersensitivity reactions.

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[1] **According to Protocol BP28179 adverse events should be captured as individual signs and symptoms on the Adverse Event eCRF rather than as a diagnosis of infusion-related reaction or allergic reaction. This required an additional analysis by the Sponsor to retrospectively identify IRRs by filtering on AEs occurring within 24 hours of infusion and drilling down to events of interest, i.e. AEs that were assessed as related to treatment with RO5520985 and suggestive of potential signs and symptoms of IRR.**

In Study BP28179, 2/115 patients (1.7%) assessed developed HAHAs upon treatment with RO5520985. The onset was for one patient treated at 10 mg/kg QW after 4 cycles and for the other patient treated at 30 mg/kg QW after 12 cycles, in both cases without any associated clinical symptoms or modification in exposure.

Potential safety concerns associated with mAb-based therapies also includes induction of immunogenicity. The immunogenicity risk for RO5520985 will be assessed through plasma samples for detection of HAHA at baseline and during and after study treatment and in the event of a hypersensitivity reaction CTCAE ≥Grade 3.

5.2.1.14 Ovarian Failure

In preclinical studies with RO5520985 in cynomolgus monkeys, pharmacology-related findings included the absence of menses, evidenced by histologically inactive ovaries and serum hormone peaks in estradiol and progesterone. Inactive endometrium was noted which correlated with a lower uterine weight. Reversibility of these findings was noted by the end of the recovery phase in all treated females.

In premenopausal women receiving bevacizumab in combination with mFOLFOX chemotherapy for adjuvant treatment for colorectal cancer, the incidence of ovarian failure was higher compared to those receiving mFOLFOX chemotherapy alone.

In clinical trials with RO5520985, no events suggestive of ovarian failure have been reported in patients.

5.2.1.15 Peripheral Edema

An increased incidence of peripheral edema has been observed in patients treated with angiopoietin-1 and -2 antagonist Fc fusion protein.

In clinical trials with RO5520985 events of edema were reported in Study BP28179: 22 events of peripheral edema in 19 patients (16.5%), 12 events of lymphedema in 11 patients (9.6%), 5 events of edema in 4 patients (3.5%) and 1 event of localized edema (0.9%). In the safety run-in of Study BP29262 there were 3 events of peripheral edema in 2/8 patients and 1 event of eyelid edema in another patient. All but one AE were non-serious. Two of the events were of Grade 3, the remaining events of Grade 1 or Grade 2. Fifteen patients had AEs that were assessed as related to treatment with RO5520985.

5.2.1.16 Pregnancy

No studies assessing the reproductive and developmental toxicity of RO5520985 have been conducted to date. It is not known whether RO5520985 can cross the placenta or cause harm to the fetus when administered to pregnant women or

whether it affects reproductive capacity. However, IgG antibodies are known to cross the placental barrier, **and angiogenesis has been shown to be critically important to fetal development. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed. Therefore, administration of RO5520985 /bevacizumab may inhibit angiogenesis in the fetus and and result in an adverse outcome of pregnancy.**

Therefore, RO5520985/bevacizumab should not be used during pregnancy. Negative pregnancy tests and highly effective means of contraception are required for patients participating in trials with RO5520985.

Based on the labeling for bevacizumab, contraceptive measures are recommended for at least 6 months following the last dose of RO5520985. Pregnancy occurring in the female partner of a man participating in the study should also be reported to the Investigator and the Sponsor.

5.2.2 Risks of 5-FU, Folinic Acid and Oxaliplatin

Safety Profile of 5-FU/folinic acid

5-FU/folinic acid should be given with care to patients who are malnourished and to those who have a history of heart disease or hepatic or renal insufficiency. The main toxicities of 5-FU are hematological toxicities, including neutropenia, thrombocytopenia, and anemia; and GI toxicities, including diarrhea, stomatitis, vomiting, and GI ulceration. GI toxicities may be exacerbated by leucovorin administration. In addition, 5-FU has been associated with ocular toxicity, including corneal epithelia erosion and excessive lacrimation; hand-foot syndrome; allergic reactions; central neurological toxicity, including acute cerebellar syndrome and nystagmus; and, rarely, cardiotoxicity, including arrhythmias, myocardial ischemia, and angina. Patients with a known dihydropyrimidine dehydrogenase deficiency or thymidylate synthase gene polymorphism who may be predisposed to 5-FU toxicity will be excluded. 5-FU may interact with warfarin. Patients should avoid prolonged exposure to sunlight because of the risk of photosensitivity during treatment with 5-FU. For a full safety profile of 5-FU, please refer to 5-Fluorouracil full prescribing information.

Folinic acid may enhance toxicities associated with 5-FU. For a full safety profile of folinic acid (e.g. Leucovorin), refer to full prescribing information of folinic acid.

Individual patients may be switched to oral capecitabine during maintenance treatment. For respective toxicity information and guidelines refer to Section 5.2.3.

Safety Profile of Oxaliplatin

In prior clinical trials of oxaliplatin, the following safety signals were identified: sensory and/or motor neuropathy, allergic reactions, pharyngolaryngeal dysesthesia, interstitial lung disease/pulmonary fibrosis, hepatotoxicity, and hematologic toxicity.

Peripheral neuropathy has not been observed to date with single-agent RO5520985. All patients must have been recovered from reversible adverse events of previous medical therapies, except alopecia prior study entry. Patients will be monitored throughout the study for new peripheral neuropathy through assessment of adverse events and physical examinations. Modifications of oxaliplatin administration in response to neuropathy are described in Section 5.2.3.3.

For more details regarding the safety profile of oxaliplatin, refer to oxaliplatin (e.g., Eloxatin®) full prescribing information.

5.2.3 Toxicity Management Guideline

5.2.3.1 General Notes

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v4.03 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the Investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the Investigator to be unlikely to develop into serious or life-threatening events, treatment will be continued at the same dose without reduction or interruption.
- In the absence of progressive disease, any delay or discontinuation of chemotherapy or biological therapy does not affect continuation of the other component(s) of study treatment.

  Oxaliplatin should be administered during Induction therapy for up to 8 Cycles but can be discontinued earlier in case of unacceptable toxicity.

  Bevacizumab and RO5520985 should be continued to progression or unacceptable toxicity for a maximum of 24 months (calculated from start of maintenance therapy) in patients who have discontinued their course of chemotherapy due to intolerable toxicity.

  Patients should continue 5-FU/leucovorin to intolerable toxicity or for a maximum of 24 months (calculated from start of maintenance therapy) in the event that they cannot tolerate bevacizumab/RO5520985.

  The doses of bevacizumab/RO5520985 will not be reduced or modified.

  Dose adjustments of bevacizumab for body weight changes are not required.

- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

- If, in the opinion of the Investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.
- No dose reductions or interruptions will be required for anemia (non-hemolytic) because it can be satisfactorily managed per treating physician's institutional guidelines.
- When a treatment cycle is temporarily interrupted because of toxicity caused by bevacizumab/RO5520985 and/or the chemotherapy regimen, the treatment cycles will be re-started such that bevacizumab/RO5520985 infusions remain synchronized with the chemotherapy.
- If it is anticipated that chemotherapy will be delayed by ≥ 2 weeks, then bevacizumab/RO5520985 should be given without the chemotherapy if there is no contraindication

5.2.3.2 Guidelines for Toxicity Management of Bevacizumab and RO5520985

Table 2 below provides a guideline how to manage certain toxicities, which are expected due to class-labeling for anti-VEGF molecules on the market including bevacizumab and on the basis of the Phase I study for RO5520985 (Study BP28179).

Temporary suspension of treatment with bevacizumab/RO5520985 must occur if a patient experiences a serious adverse event or Grade 3 or 4 nonserious adverse event that is

1) Not addressed by Table 2

and

2) Assessed by the Investigator as related to bevacizumab/RO5520985.

If the event resolves to Grade ≤ 1 within or equal to 42 days,-bevacizumab/RO5520985 may be restarted at the same dose level. If bevacizumab/RO5520985 is delayed for >42 days due to toxicity, the patient must be permanently discontinued from bevacizumab/RO5520985 therapy.

It should be noted that the 42-day window for resolution of toxicity begins on the day that the decision is made to delay a scheduled administration of bevacizumab/RO5520985 and not on the day that the study drugs were most recently administered.

The appropriate interval between the last dose of bevacizumab/RO5520985 and major surgery is unknown. The half-life of bevacizumab and RO5520985 is approximately 21 and 9 days, respectively. For the purpose of the blinded study elective surgery should be delayed whenever possible, but if necessary, bevacizumab/RO5520985 should be held for at least 28 days prior to the procedure. Re-initiation of bevacizumab/RO5520985 following surgery should not occur for at least 28 days and until wounds have fully

healed. Re-initiation of bevacizumab/ RO5520985 after surgery requires documented approval from the Medical Monitor.

The site should advice their study patients to immediately contact the Investigator in case they experience clinical symptoms suggestive of intestinal sub-/occlusion/intestinal obstruction or GI-perforation such as acute, persisting and/or increasing abdominal pain, nausea and vomiting, etc. in order to initiate the appropriate diagnostic (incl. physical examination, laboratory tests and abdominal imaging) and therapeutic (incl. non-/surgical procedures) measures for this condition. It is also recommended to perform endoscopic evaluation in any patient during treatment with RO5520985/bevacizumab upon presentation with symptoms that may be related to a GI ulcer.

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985

Dose Management for Adverse Events

Event	Action to Be Taken
Hypertension	
Grade 1 or 2	No study treatment modifications
Grade 3	If not controlled to 150/100 mmHg by medication within 14 days, discontinue bevacizumab/RO5520985
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab/RO5520985
Hemorrhage	
Grade 1 or 2 non-pulmonary or non-CNS events	No study treatment modifications
Grade 3 non-pulmonary or non-brain or non-spinal cord hemorrhage	Patients will have bevacizumab/RO5520985, and chemotherapy held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable within 14 days after onset • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab/RO5520985
Grade 4 non-pulmonary or non-brain or non-spinal cord hemorrhage	Discontinue bevacizumab/RO5520985
Grade 1 pulmonary or brain or spinal cord hemorrhage	Patients will have bevacizumab/RO5520985, and chemotherapy held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable within 14 days after onset • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence
Grade 2, 3, or 4 pulmonary or brain or spinal cord hemorrhage	Discontinue bevacizumab/RO5520985

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985 (cont.)

Venous thromboembolic event	
Grade 1 or 2 not requiring full−dose anti-coagulation	No study treatment modifications
Grade 2 or 3, requiring full−dose anti-coagulation ≤14 days	If duration of full-dose anticoagulation is ≤14 days , bevacizumab/RO5520985, and chemotherapy should be held until the full-dose anticoagulation period is over.
Grade 3, requiring full-dose anti-coagulation >14 days	**If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab/RO5520985 and chemotherapy may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met:** • **LMWH or other anticoagulant dosing must be stable prior to restarting study treatment.** • **The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.**
Grade 4	Discontinue bevacizumab/RO5520985
Arterial thromboembolic event (New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
≥ Grad 3	Discontinue bevacizumab/RO5520985
Thrombotic microangiopathy (A pathological process of microvascular thrombosis, consumptive thrombocytopenia and microangiopathic haemolytic anaemia leading to end-organ ischaemia and infarction)	
Any Grade	Discontinue bevacizumab/RO5520985

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985 (cont.)

Left ventricular systolic dysfunction/ Congestive heart failure	
Grade 1 or 2	No study treatment modifications
Grade ≥ 3	Discontinue bevacizumab/RO5520985

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985 (cont.)

Proteinuria	
Grade 1 (urine dipstick 1 + or urine collection 0.15 to 1.0 g/24 hrs)	No study treatment modifications
Grade 2 (urine dipstick 2 + to 3 + or urine collection > 1.0 to 3.5 g/24 hrs)	For 2 + dipstick, may administer bevacizumab/RO5520985 and obtain 24-hrs urine prior to next dose of bevacizumab/RO5520985. For 3 + dipstick, obtain 24-hrs urine prior to administration of bevacizumab/RO5520985. Hold bevacizumab/RO5520985 treatment for proteinuria ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hrs [a]
Grade 3 (urine dipstick 4 + or urine collection > 3.5 g/24 hrs)	Hold bevacizumab/RO5520985 treatment. Resume when proteinuria is < 2 g/24 hrs [a]
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab/RO5520985
GI perforation	
Any grade	Discontinue bevacizumab/RO5520985
Fistula	
Any grade fistula involving an internal organ	Discontinue bevacizumab/RO5520985
Confirmed sub occlusive/occlusive syndrome/intestinal obstruction (Ileus)	
Any grade	Discontinue bevacizumab/RO5520985
Wound healingcomplication	
Grade 1 or 2	No study treatment modifications
Grade 3, requiring surgical intervention	Discontinue bevacizumab/RO5520985
Grade 4	Discontinue bevacizumab/RO5520985
GI-ulcer	
Grade 1 or 2	**Withold study drug treatment with bevacizumab/RO5520985. Resume when ulcer resolves to Grade 0.**

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985 (cont.)

Grade ≥ 3	**Discontinue bevacizumab/RO5520985**
Entero-/Colitis	
Grade 1	**No study treatment modifications**
Grade 2 and 3	**Withold study drug treatment with bevacizumab/RO5520985. Resume when colitis improves to Grade 0 or 1**
Grade 4	**Discontinue bevacizumab/RO5520985**

Table 2 Toxicity Management Guideline for Bevacizumab and RO5520985 (cont.)

Posterior reversible encephalopathy syndrome	
Any grade (confirmed by MRI)	Discontinue bevacizumab/RO5520985
Infusion-related reaction (IRR)	If an IRR develops, the infusion of RO5520985/bevacizumab should be temporarily slowed down or interrupted. The patient should be monitored until complete resolution of the symptoms and treated as clinically indicated. Treatment or concomitant medication may include acetaminophen/ paracetamol, antihistamine, IV saline, oxygen, bronchodilators, corticosteroids and vasopressors depending on the symptoms. If the infusion is interrupted: • In the event of IRR CTCAE Grade 1, upon resolution of symptoms, the infusion will resume at the same rate (the rate being used at the time that the IRR occurred) • In the event of IRR CTCAE Grade 2, upon resolution of symptoms, the infusion will resume at one-half the previous rate. • In the event of IRR CTCAE Grade 3 or CTCAE Grade 4 (which may include pulmonary or cardiac events) or an anaphylactic reaction, the infusion must be stopped and the patient should receive aggressive treatment. Patients experiencing IRR CTCAE Grade 4 must be permanently discontinued from study drug treatment. For patients who already experienced IRR CTCAE ≥ Grade 2, the infusion rate for all subsequent RO5520985/bevacizumab infusion, should be reduced at one-half of the previous rate and premedication may be given 30 minutes prior to infusion including: • Paracetamol (500−1000 mg) • H_1-receptor antagonist e.g., diphenhydramine (25−50 mg PO or IV) or an alternative anti-histamine at an adequate dose • Hydrocortisone (200 mg IV) or equivalent dose of another corticosteroid as clinically indicated • H_2-receptor antagonist (e.g., ranitidine; cimetidine) as clinically indicated

CNS = central nervous system; GI = gastrointestinal; INR = international normalized ratio; IRR = infusion-related reaction; IV = intravenous; LMWH = low molecular weight heparin; MRI = magnetic resonance imaging; PO = per os/by mouth.

[a] All proteinuria values are from 24-hour urine.

5.2.3.3 Guidelines for Toxicity Management of FOLFOX

Dose modifications listed below are guidelines for the management of chemotherapy–specific toxicities. The treating physician may use discretion in modifying or accelerating the dose modification guidelines described below, depending upon the severity of toxicity and an assessment of the risk versus benefit for the patient with the goal of maximizing patient compliance and access to supportive care.

If oxaliplatin treatment is discontinued, patients are encouraged to continue chemotherapy with 5-FU/folinic acid + bevacizumab/RO5520985. Then, if 5-FU/folinic acid are discontinued, patients should continue to take bevacizumab/RO5520985 treatment until documented progressive disease or unacceptable toxicity for a maximum of 24 months.

Patients who experience chemotherapy-related toxicities < Grade 3 that are intolerable may discontinue chemotherapy treatment at the discretion of the Investigator. For these patients, RO5520985 and bevacizumab should continue.

Once chemotherapy is discontinued completely, it cannot be restarted. All patients will continue protocol-specified tumor assessments until documented progressive disease and will then have follow-up assessments for OS and subsequent anticancer therapy.

Dose adjustments at the start of each 14-day cycle will be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Once a dose reduction is made, the dose will not be re-escalated during subsequent cycles (Table 3 for chemotherapy dose reduction levels).

Patients who require reductions below the –2 dose level should be discontinued from that chemotherapy agent. If the recommended action below in response to a specific toxicity is not applicable (e.g., oxaliplatin was previously discontinued), the action recommended for the next occurrence of that toxicity should be followed.

Table 3 FOLFOX Dose Adjustment

	Oxaliplatin	5-FU Bolus	5-FU Infusion
Starting Dose mg/m^2	85	400	2400
–1 Dose Level mg/m^2	65	0	2000
–2 Dose Level mg/m^2	50	0	1600

FU = 5-fluorouracil.

Modifications for Hematologic Toxicity

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged

to seek medical attention at the earliest opportunity. Colony stimulating factors may be used as detailed in Section 4.5.1.

Chemotherapy treatment should not be administered until ANC ≥ 1000/μL and platelets ≥ 75,000/μL.

For Grade 4 neutropenia or febrile neutropenia, Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or a >2 week dose delay due to prolonged ANC or platelet recovery (to ANC ≥ 1000/μL and platelets ≥ 75,000/μL):

- First occurrence: Omit the bolus dose of 5-FU permanently and reduce infusional 5-FU and oxaliplatin by one dose level each for subsequent cycles
- Second occurrence: Reduce infusional 5-FU and oxaliplatin by an additional dose level each for subsequent cycles
- Third occurrence: Discontinue chemotherapy, continue bevacizumab/ RO5520985

For the first occurrence of Grade 3 neutropenia without fever or Grade 3 thrombocytopenia without bleeding, the 5-FU bolus should be omitted permanently. If hematologic toxicity recurs, consideration should be given to reducing the doses of infusional 5-FU and oxaliplatin for subsequent cycles.

Chemotherapy should be discontinued if ANC and platelets do not recover to ≥1000/μL and ≥ 75,000/μL, respectively, after treatment is delayed by 3 weeks.

Modifications for Oxaliplatin-Induced Neurotoxicity

For neuropathy (sensory, motor, or cranial neuropathy, as graded per Table 4) attributed to oxaliplatin dose modifications should be carried out as follows:

- For Grade 1 neuropathy at the time of planned re-treatment: continue planned treatment.
- For Grade 2 neuropathy at the time of planned re-treatment or Grade 3 at any time:

  First occurrence: Withhold oxaliplatin until symptoms resolve (up to 2 weeks) to Grade ≤1 and then reduce the dose of oxaliplatin 1 dose level

  Second occurrence: Withhold oxaliplatin until symptoms resolve (up to 2 weeks) to Grade ≤1 and then reduce the dose of oxaliplatin 1 dose level

  Third occurrence, requirement to reduce oxaliplatin dose below –2 dose level or failure to resolve to Grade 1 within 2 weeks: Discontinue oxaliplatin
- For Grade 4 neuropathy occurring at any time, discontinue oxaliplatin therapy.

Table 4 Adverse Event Grading for Neuropathy

Grade	Description
1	Asymptomatic; loss of deep tendon reflexes or paresthesia
2	Moderate symptoms; limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL = activities of daily living.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

If pseudolaryngopharyngeal dysesthesia occurs, subsequent doses of oxaliplatin may be administered as a 6-hour infusion, and folinic acid should be administered during the last 2 hours of infusion.

Modifications for Other Nonhematologic Toxicity

For other Grade 3 or 4 or persistent intolerable Grade 2 nonhematologic toxicity (e.g., fatigue, diarrhea, hand-foot syndrome, hepatic toxicity, respiratory symptoms, etc.) attributed to chemotherapy, chemotherapy can be held until adverse event resolution (Grade $\leq$ 1) for up to a maximum of 4 weeks.

- First occurrence: omit the bolus dose of 5-FU permanently, reduce the 5-FU infusional dose 1 dose level and/or reduce oxaliplatin 1 dose level for subsequent cycles
- Second occurrence of Grade 4 toxicity: discontinue the chemotherapy regimen, continue bevacizumab/RO5520985
- Second and third occurrences of Grade 3 or intolerable Grade 2 toxicity: if indicated reduce the 5-FU infusional dose 1 dose level and/or reduce oxaliplatin 1 dose level for subsequent cycles
- Fourth occurrence of Grade 3 or intolerable Grade 2 toxicity: discontinue the chemotherapy regimen, continue bevacizumab/RO5520985

No dose reduction should be made for Grade 1 and 2 toxicities, except for those considered intolerable to the patient due to prolonged duration or adverse effects on quality of life.

When oxaliplatin is discontinued (i.e., post Cycle 8 or due to toxicity), 5-FU and folinic acid should be continued to disease progression or intolerable toxicity. Oxaliplatin should not be restarted after being discontinued on this study.

Any contraindications and special warnings and precautions for the use of FOLFOX should be observed, and any medication(s) or therapy(ies) contraindicated in the full

prescribing information of 5-FU and oxaliplatin are contraindicated in patients receiving 5-FU and oxaliplatin.

Patients may be premedicated with 5-HT3 receptor antagonists or other standard of care methods to control nausea and vomiting. For symptoms of diarrhea and/or abdominal cramping, patients should be instructed to begin taking loperamide 2 mg orally at the time of the first liquid stool and continue 2 mg approximately every 2 hours until at least 12 hours after the last liquid stool, with oral rehydration. Calcium and magnesium salts may be administered to patients with acute symptomatic neurotoxicity at the discretion of the treating physician.

Other Toxicity

For any Grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to Grade 1 toxicity for up to a maximum of 4 weeks.

5.2.3.4 Guidelines for Toxicity Management of Capecitabine (Xeloda®)

During induction phase substitution of 5-FU/folinic acid is not permitted. During the maintenance phase substitution of 5-FU/folinic acid IV by oral capecitabine is discouraged. However, individual patients may receive capecitabine without folinic acid according to institutional standards (e.g., 625 mg/m2 bid continuously) at the discretion of the Investigator and in agreement with the Sponsor's medical monitor.

Patients treated with capecitabine should be carefully monitored for toxicity. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may have to be withheld or reduced. Most common adverse reactions (≥ 30%) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia.

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the capecitabine dose (treatment interruption or dose reduction). Once the dose has been reduced it should not be increased at a later time.

For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening treatment can be continued at the same dose without reduction or interruption. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced. Table 5 shows the recommended dose modifications following toxicity related to capecitabine.

Table 5 Recommended Dose Modifications of Capecitabine

Grade [a]	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0 - 1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Interrupt until resolved to Grade 0–1	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4		
1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0–1	50%
2nd appearance	Discontinue permanently	Not applicable

[a] According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0.

Please note the following warnings and precautions associated with capecitabine:

- Diarrhea: May be severe. Interrupt capecitabine treatment immediately until diarrhea resolves or decreases to Grade 1. Recommend standard anti-diarrheal treatments.
- Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled.
- Hand-and-Foot Syndrome (Grade 2 or 3): Interrupt capecitabine treatment until the event resolves or decreases in intensity.
- Hyperbilirubinemia (Grade 2–4): Interrupt capecitabine treatment immediately until the hyperbilirubinemia resolves or decreases in intensity.

- Severe skin reactions: Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to capecitabine treatment.
- Hematologic: Do not treat patients with neutrophil counts $<1.5 \times 10^9$/L or thrombocyte counts $<100 \times 10^9$/L. If Grade 3–4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.

For more details regarding the safety profile ofpecitabine, refer to full prescribing information of Capecitabine (Xeloda®).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (Section 5.2.1.16 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (Section 5.1.2 for seriousness criteria), severity (Section 5.3.3), and causality (Section 5.3.4).

5.3.1 Adverse Event/Serious Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all adverse events/serious adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug.

After a period of 28 days from the last dose of study drug, Investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (Section 5.5).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.03), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (Section 5.3.7 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (Section 5.3.7 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of nontreatment-related factors that are known to be associated with the occurrence of the event

For patient receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion **and are judged to be related to study drug infusion** should be captured as a diagnosis (e.g. infusion related reaction **or anaphylactic reaction as appropriate**), **on the Adverse Event eCRF. In addition the individual signs and symptoms should be reported on the comment section of the Adverse Event eCRF.**

Other Adverse Events

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

Patients who have Liver Metastases

For patients who have liver metastases, the conditions set out below apply.

The finding of an elevated ALT or AST ($> \mathbf{5} \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> \mathbf{5} \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $> \mathbf{5} \times$ baseline value in combination with clinical jaundice

Patients who do not have Liver Metastases

For patients who do not have liver metastases, the conditions set out below apply.

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (Section 5.3.7).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (Section 5.3.5.7) that are attributed by the Investigator solely to progression of CRC should be recorded only on the End of Study Visit eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (Section 5.3.5.7).

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 Adverse Event eCRF. Generally, only one such event should be reported. The term "**sudden death**" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient 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 Adverse Event 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 post-study survival follow-up, deaths attributed to progression of CRC should be recorded only on the Disease and Survival Folllow-up eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of Colorectal Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.2), except as outlined below.

The following hospitalization scenarios are **not** considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol, e.g., for study drug administration or insertion of access device for study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization due to secondary resection

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.3.7 and Section 5.4).

5.3.6 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Responsible contact information will be distributed to all Investigators ("Protocol Administrative and Contact Information & List of Investigators").

5.3.7 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events (Sections 5.1.2 and 5.3.7), Investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the SAE Responsible within 24 hours.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to (Appendix 7).

5.3.8 Reporting Requirements for Pregnancies

5.3.8.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 6 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.3.8.2 Pregnancies in Female Partners of a Male Patient

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy.

Once the authorization has been signed, the Investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.3.8.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.3.7).

5.3.8.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.3.7).

5.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.4.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.3.8.

5.4.2 Sponsor Follow-Up

For serious adverse events and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.5 POST-STUDY ADVERSE EVENTS

At the study completion/early termination visit, the Investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug). However, the Sponsor should be notified if the Investigator becomes aware of any death, other serious adverse event occurring after the end of the adverse event reporting period, **if the event is believed to be related to prior study drug treatment.** The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report the event directly to Roche Safety Risk Management via telephone ("Protocol Administrative and Contact Information & List of Investigators").

During post-study survival follow-up, deaths attributed to progression of CRC should be recorded only on the Survival eCRF.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- RO5520985: Investigator's Brochure; DSCI
- Local prescribing information for bevacizumab,

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The data will be analyzed by the Sponsor and/or designated CRO. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy, safety, pharmacokinetics and biomarkers observations and measurements. The core analysis will be based on all patients data up to the time when approximatelly 80 events (PFS) have been observed in Part II of the study. The additional data for any patient continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in subsequent extension report once the study is terminated.

6.1 DETERMINATION OF SAMPLE SIZE

This Phase II trial is designed to make a preliminary evaluation of the efficacy and safety of RO5520985 plus mFOLFOX-6 versus bevacizumab plus mFOLFOX-6 in patients with previously untreated mCRC.

Within Part I, 6 -18 patients will be treated with RO5520985 plus mFOLFOX-6. Six patients per RO5520985 dose to be tested is considered sufficient to assess the safety and tolerability of RO5520985 in combination with mFOLFOX-6.

Part II of the study will enroll approximately 190 patients, and the primary analysis will be performed after approximately 80 investigator assessed PFS events. If the drop-out rate is higher than expected, additional patients might be enrolled to ensure sufficient data to evaluate the efficacy and safety profile of the investigational treatment.

The emphasis of the efficacy analysis will be on estimation of the magnitude of treatment effect rather than hypothesis testing. This trial is hypothesis-generating and is designed to be able to detect a meaningful benefit of the combination therapy of RO5520985 plus mFOLFOX-6 versus bevacizumab plus mFOLFOX-6. Based on the sample size of 80 events observed in the two treatment arms combined, there is an 80% power to detect a HR of 0.574 at a one-sided significance level of 0.05.

6.2 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used in evaluating the conduct of the study. Enrollment, study treatment administration, and discontinuations from the study will be summarized by part and treatment arm. Listing of major protocol deviations will be produced.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

The safety analysis population will include all patients (Part I and Part II) who receive any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985). Patients will be assigned to the treatment arm received.

6.3.2 Pharmacokinetic Analysis Population

PK analyses will include all patients who received any amount of study treatment (5-FU/folinic acid, oxaliplatin, bevacizumab, or RO5520985), the same as the safety analysis population.

Patients may be excluded from the PK analysis population if they significantly violate the eligibility criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the pharmacokinetic analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.3.3 Efficacy Analysis Population

Primary and secondary efficacy analyses will be based on the intent to treat (ITT) population. It will include all patients who were randomized (Part II only) and received any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985). Patients will be assigned to the treatment arm to which they were randomized.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (e.g., age and sex) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by "overall" patient population and by treatment arm within each part.

Exposure to study medications will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics. Dose interruptions and their reasons will be presented by schedule and dose level.

6.5 SAFETY ANALYSES

Safety analysis will be performed for all the patients in the safety analysis population. All safety parameters will be analyzed using descriptive statistics, summarized and presented in tables.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the Investigator for adverse events will be standardized by the Sponsor. Adverse events will be listed and summarized by mapped term and appropriate thesaurus level.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patients listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International

d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

For laboratory data, summary tables of change from baseline over time based on SI (Standard International) units will be displayed. Shifts in toxicity grade from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. Additional figures/tables/listings may be produced as deemed appropriate.

6.5.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges (e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin). Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.5.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included the local laboratory reference ranges will be used. In the event that the local laboratory does not have laboratory reference ranges, the Roche predefined standard reference range will be used. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the patient's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as "HH" for very high or "LL" for very low.

6.5.3 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate. Additional figures/tables/listings may be produced as deemed appropriate.

6.5.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.5.5 Concomitant Medications

The original terms recorded on the patients' eCRF by the Investigator for concomitant medications will be standardized by the sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 EFFICACY ANALYSES

The primary analysis and secondary analysis will be based on the efficacy analysis population. The core analysis will be based on all patients data up to the time when approximatelly 80 events (PFS) have been observed in Part II of the study. The additional data for any patient continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in subsequent extension report once the study is terminated.

6.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is PFS. PFS is defined as the time between randomization and the date of first documented disease progression or death from any cause on study, whichever occurs first. Progression will be based on tumor assessment made by the Investigator according to RECIST 1.1 criteria (Appendix 8). Death on study is defined as death from any cause within 30 days of the last study treatment.

Patients without an event on study will be censored at the date of the last tumor assessment when the patient was known to be progression free either during follow up or during study treatment. Patients without or unknown post baseline assessments but known to be alive will be censored at day of randomization plus 1. Kaplan-Meier methods will be used to estimate median PFS for each treatment arm. The stratified Cox proportional hazard model will be used to estimate the hazard ratio (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval. The stratification factors are number of metastatic sites (1 vs.> 1) and country/region. Results from a stratified and unstratified log-rank test will also be presented

6.6.2 Secondary Efficacy Endpoints

Objective Response Rate (ORR)

Objective response rate (ORR) is determined as the rate of patients with an objective tumor response (complete [CR] or partial response [PR]). Objective response (OR) is defined as a complete or partial response as determined by the Investigator using RECIST v1.1 on two consecutive occasions at least 4 weeks apart. Patients without a post-baseline tumor assessment will be regarded as nonresponders. An estimate of the objective response rate and 95% confidence intervals (Casella 1986) will be calculated for each treatment arm. Confidence intervals for the difference in objective response rate will be calculated.

Duration of Objective Response (OR)

For patients with an OR, duration of OR is defined as the time from the initial response (CR or PR) to disease progression or death from any cause on study. This will only be calculated for patients who have a best overall response of CR or PR. Methods for handling censoring and for analysis are the same as those described for PFS. No adjustments will be made to account for the non-random nature of this comparison.

Overall Survival (OS)

OS is defined as the time from randomization until death from any cause. All deaths will be included, without regard to whether they occur on study or following treatment discontinuation. For patients who have not died, OS will be censored at the last date known to be alive. Patients without any post baseline information will be censored at the time of randomization. Analysis methods are the same as those described for PFS.

Subgroup analyses of the above endpoints (primary and secondary) will be performed to evaluate the clinical outcome for important clinical covariates. Details of the sub group analyses will be provided in the statistical analysis plan.

6.7 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker parameters may be presented by listings and descriptive summary statistics separately by treatment arms.

All analyses of PD and exploratory biomarkers will be based on the safety analysis population, in other words, any patients who received any amount of study treatment (5-FU/folic acid, oxaliplatin, bevacizumab, or RO5520985).

For the analysis of PD biomarkers the primary evaluation will be based on the observed change from baseline. Both actual values and estimated parameters will be presented in summary tables and graphically.

To assess predictability of a biomarker, the association between clinical outcome and the biomarker level or changes thereof will be explored. Details of the biomarker analysis will be provided within the Statistical Analysis Plan (SAP).

6.8 PHARMACOKINETIC ANALYSES

All pharmacokinetic parameters will be presented by listings and descriptive summary statistics separately by group or cohorts.

Individual and mean plasma RO5520985, oxaliplatin (free and total), and 5-FU concentration versus time data will be tabulated and plotted. The plasma pharmacokinetics of RO5520985, oxaliplatin, and 5-FU will be summarized by estimating total exposure (area under the curve [AUC]), maximum concentration, total clearance, volume of distribution at steady–state, and terminal half-life (when applicable). These parameters will be tabulated and summarized (arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum). Interpatient variability and drug accumulation will be evaluated.

Additional PK analyses will be conducted as appropriate.

6.9 OTHER EXPLORATORY ANALYSES

PK/PD Modeling

Exploratory graphical analyses of exposure-efficacy relationships may be produced for selected efficacy, PD and/or safety measurements if feasible. A PK/PD modeling approach may be considered in order to further explore the exposure-response relationship of selected response variables.

Tumor Growth Kinetics

An exploratory assessment of tumor growth kinetics will be made by comparing post-treatment scans with at least 2 pre-treatment scans not older than 12 weeks prior to C1D1, if available. The two pre-treatment scans consists of a pre-study scan (if available) and the study baseline scan, and will allow estimation of tumor growth rate before start of treatment. If the pre-treatment tumor growth kinetic can be assessed, this will then be compared to the growth/shrinkage rate after start of treatment. Data will be explored using linear and/or exponential models, as appropriate, in non linear mixed effect modelling software.

6.10 INTERIM ANALYSES

As decribed in Section 3.1.2 interim safety analysis of Part I patients will be performed by an Safety IMC after all patients have received at least two full cycles. The Safety IMC may also conduct further reviews based on safety signals that arise at any time during Part II of the study. Details of the interim safety analysis will be described in the Safety IMC charter. The purpose of the Safety IMC is to facilitate a formal review of the safety data, but the Safety IMC is not an external data monitoring committee. It will consist of at least a Sponsor Translational Medicine Leader/Clinical Scientist, Safety Scientist/Safety Science Leader, Statistical Programming Analyst (SPA) and Biostatistician.

Within Part II of the study, an interim analysis for futility is planned to be conducted after approximately 30 PFS events. A cut-off HR of 1.0 has been suggested as non binding futility criteria. The probability of observing an HR equal or higher than 0.77 at final analysis, given an HR of 1.0 at the interim analysis, will be above 80%. Enrollment will not be stopped during the interim analysis. Administrative interim analysis, based on efficacy, may also be performed during Part II of the study after approximately 30 events and again after approximately 50 events. The results will be used by the Sponsor solely for the decision making regarding activities for further clinical development of the compound under investigation. The study will not be stopped for efficacy.

Separate from the Safety IMC, there will be in addition an Efficacy IMC responsible for the futility/efficacy analysis of Part II. The details and modalities are described in a pre-specified charter outlined in a separate document as well as in the statistical analysis plan.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Handling Manual that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an online EDC system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the principal Investigator or authorized delegate from the study staff. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment–limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor/CRO in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

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

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should

maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, patient to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Informed Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Informed Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness

of the patient to participate. The final revised IRB/EC-approved Informed Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Informed Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Informed Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Informed Consent Forms for continued participation in the study.

A copy of each signed Informed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Informed Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Informed Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, Investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV, or the date at which the last data point from the last patient, which is required for statistical analysis is received, whichever is the later date.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit a Development Safety Update Report (DSUR) once a year to the EC and CAs according to local regulatory requirements and timelines of each country participating in the study.

Sampling for the RCR is contingent on review and approval for the exploratory biomarker assessments and written informed consent by an appropriate regulatory body

(depending on the country where the study is performed) and a site's IRB/EC. If a regulatory or site's IRB/EC does not approve the sampling for the exploratory assessments the section on biomarker sampling will not be applicable.It is the understanding of the sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an IRB. This board must operate in accordance with the current Federal Regulations. The sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments/modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

The sponsor of the trial is F. Hoffmann-La Roche Ltd. The study will be managed by F. Hofmann-La Roche Ltd. and a Contract Research Organisation (CRO). The CRO will provide clinical operations and data management. Approximately 50 sites in approximately 7−10 countries will participate to enroll approximately 200 - 210 patients.

The study is divided in 2 parts: Part I of the study is single-arm, open-label and will assess the safety of RO5520985 in combination with mFOLFOX-6 in 6-18 patients prior embarking to the randomized part of the study. Part II is parallel arm, double-blind and patients will be randomized in a ratio of 1:1 to receive either RO5520985 plus mFOLFOX-6 (experimental arm) or bevacizumab plus mFOLFOX6 (control arm). The study site will obtain the patient's unique identification number and treatment assignment from the IxRS.

Central laboratories will be used for a subset of laboratory assessments.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally

support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

10. REFERENCES

Abu-Hejleh T, Mezhir JJ, Goodheart MJ et al. Incidence and management of gastrointestinal perforation from bevacizumab in advanced canver. Curr Oncol Rep (2012) 14:277–284.

Alberts SR, Wagman LD. Chemotherapy for colorectal cancer liver metastases. The Oncologist 2008;13:1063–73.

Arnold D, Seufferlein T. Targeted treatments in colorectal cancer: state of the art and future perspectives. Gut 2010; 59: 838–58.

Bach F, Uddin FJ and Burke D. Angiopoietins in malignancy. Eur J Surg Oncol. 2007;33:7–15.

Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab andpanitumumab in colorectal cancer. J Clin Oncol. 2010;28:1254-61.

Benson AB 3rd, Bekaii-Saab T, Chan E, et al. Metastatic colon cancer, version 3.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2013;11:141-52.

Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer. 2003;3:401–10.

Bergers G, Brekken R, McMahon G, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol. 2000;2:737-44.

Brockton NT, Klimowicz AC, Bose P, et al. High stromal carbonic anhydrase IX expression is associated with nodal metastasis and decreased survival in patients with surgically-treated oral cavity squamous cell carcinoma. Oral Oncol. 2012;48:615-22.

Brown JL, Cao ZA, Pinzon-Ortiz M, et al. A human monoclonal anti-ANG2 antibody leads to broad antitumor activity in combination with VEGF inhibitors and chemotherapy agents in preclinical models. Mol Cancer Ther. 2010;9:145-56.

Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487:330-7.

Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med. 2001;7:575-83.

Cascone T and Heymach JV. Targeting the Angiopoietic/Tie2 Pathway: Cutting Tumor Vessels With a Double-Edged Sword? J Clin Oncol. 2012;30:441–4.

Casella G. Refining binomial confidence intervals. Can J Stat 1986;14:113–29.

Chung YC, Hou YC, Chang CN et al. Expression and prognostic significance of angiopoietin in colorectal carcinoma. J Surg Oncol. 2006;94:631-8.

Coxon A, Rex K, Sun J et al. Combined treatment of angiopoietin and VEGF pathway antagonists enhances antitumor activity in preclinical models of colon carcinoma. AACR abstract 2008.

De Palma M, Naldini L. Angiopoietin-2 TIEs up macrophages in tumor angiogenesis. Clin Cancer Res. 2011;17:5226-32.

Deprimo SE, Bello CL, Smeraglia J, et al. Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. J Transl Med. 2007;5:32.

Deschoolmeester V, Baay M, Lardon F, Pauwels P, Peeters M. Immune Cells in Colorectal Cancer: Prognostic Relevance and Role of MSI. Cancer Microenviron. 2011;4:377-92.

Diehl F, Li M, Dressman D, He Y, et al. Detection and quantification of mutations in the plasma of patients with colorectal tumors. Proc Natl Acad Sci U S A. 2005;102:16368-73.

Dieras V, Jassem J, Dirix L t al. A randomized, placebo-controlled phase II study of AMG 386 plus bevacizumab (Bev) and paclitaxel (P) or AMG 386 plus P as first-line therapy in patients (pts) with HER2-negative, locally recurrent or metastatic breast cancer (LR/MBC). J Clin Oncol 29: 2011; (suppl; abstr 544).

Drevs J, Siegert P, Medinger M. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2007;25:3045-54.

Etoh T, Inoue H, Tanaka S, Barnard GF, Kitano S, Mori M. Angiopoietin-2 is related to tumor angiogenesis in gastric carcinoma: possible in vivo regulation via induction of proteases. Cancer Res. 2001;61:2145-53.

Falcon BL, Hashizume H, Koumoutsakos P, et al. Contrasting actions of selective inhibitors of angiopoietin-1 and angiopoietin-2 on the normalization of tumor blood vessels. Am J Pathol. 2009;175:2159-70.

Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25:581–611.

Fiedler U, Scharpfenecker M, Koidl S, et al. The Tie-2 ligand angiopoietin-2 is stored in and rapidly released upon stimulation from endothelial cell Weibel-Palade bodies. Blood 2004;103:4150-6.

Foernzler D, Delmar P, Kockx M, et al. Tumor tissue based biomarker analysis in NO16966: A randomized Phase III study of first-line bevacizumab in combination with oxaliplatin-based chemotherapy in patients with mCRC. 2010 Gastrointestinal Cancers Symposium. Abstract 374.

Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012;12:298-306.

Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25:4779–86.

Funada Y, Noguchi T, Kikuchi R, Takeno S, Uchida Y, Gabbert HE. Prognostic significance of CD8+ T cell and macrophage peritumoral infiltration in colorectal cancer. Oncol Rep. 2003;10:309-13.

Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313:1960-4.

Garden OJ, Rees M, Poston GJ et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006;55(Suppl 3): iii1–iii8.

Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and lucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology group study E3200. J Clin Oncol. 2007;25:1539–1544.

Goede V, Coutelle O, Neuneier J, et al. Identification of serum angiopoietin-2 as a biomarker for clinical outcome of colorectal cancer patients treated with bevacizumab–containing therapy. Br J Cancer. 2010;103:1407–14.

Grothey A and Allegra C. Antiangiogenesis therapy in the treatment of metastatic colorectal cancer. Ther Adv Med Oncol. 2012;4:301–19.

Hashizume H, Falcón BL, Kuroda T, et al. Complementary actions of inhibitors of angiopoietin-2 and VEGF on tumor angiogenesis and growth. Cancer Res. 2010;70:2213-23.

Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol. 2005;23:1011–27.

Horowitz NS, Penson RT, Duda DG, et al. Safety, Efficacy, and Biomarker Exploration in a Phase II Study of Bevacizumab, Oxaliplatin, and Gemcitabine in Recurrent Müllerian Carcinoma. Clin Ovarian Cancer Other Gynecol Malig. 2011;4:26-33.

Huang H, Bhat A, Woodnutt G, et al. Targeting the ANGPT-TIE2 pathway in malignancy. Nat Rev Cancer. 2010;10:575–85.

Huang H, Lai JY, Do J, et al. Specifically Targeting Angiopoietin-2 Inhibits Angiogenesis, Tie2-Expressing Monocyte Infiltration, and Tumor Growth. Clin Cancer Res 2011;17:1001–11.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.

Hurwitz H. New Combinations in Metastatic Colorectal Cancer. What Are Our Expectations? The Oncologist 2005; 10: 320-322.

Hurwitz H, Tebutt N, Kabbinavar F et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. Oncologist. 2013;18:1004–12.

Imanishi Y, Hu B, Jarzynka MJ, et al. Angiopoietin-2 stimulates breast cancer metastasis through the α5β1 integrin-mediated pathway. Cancer Res. 2007;67:4254-63.

Imbulgoda A, MacLean A, Heine J et al. Colonic perforation with intraluminal stents and bevacizumab in advanced colorectal cancer: retrospective case series and literature review. 2015 Can J Surg, 58, 167-171.

Itoh T, Tanioka M, Yoshida H, et al. Reduced angiogenesis and tumor progression in gelatinase A-deficient mice. Cancer Res. 1998;58:1048-51.

Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. J Clin Oncol. 2006;24:217-27.

Kabbinavar F, Hambleton J, J, Mass RD, et al. Combined analysis of efficacy: the addition of bevaccizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005;23:3706-12.

Kang JC, Chen JS, Lee CH, Chang JJ, Shieh YS. Intratumoral macrophage counts correlate with tumor progression in colorectal cancer. J Surg Oncol. 2010;102:242-8.

Khorana AA, Ryan CK, Cox C, Eberly S, Sahasrabudhe DM. Vascular endothelial growth factor, CD68, and epidermal growth factor receptor expression and survival in patients with Stage II and Stage III colon carcinoma: a role for the host response in prognosis. Cancer. 2003;97:960-8.

Kienast Y, Klein C, Scheuer W, et al. Ang-2-VEGF-A CrossMab, a novel bispecific human IgG1 antibody blocking VEGF-A and Ang-2 functions simultaneously mediates potent anti-tumor, anti-angiogenic, and anti-metastatic efficacy. Clin Cancer Res. 2013;19; 6730–40.

Klimowicz AC, Bose P, Petrillo SK, et al. The prognostic impact of a combined carbonic anhydrase IX and Ki67 signature in oral squamous cell carcinoma. Br J Cancer. 2013;109:1859-66.

Koh GY. Orchestral actions of angiopoietin-1 in vascular regeneration. Trends Mol Med. 2013;19:31-9.

Koopmann M et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG). J Clin Oncol 31, 2013 (suppl; abstr 3502) and oral presentation at ASCO 2013.

Kubicka S, Von Moos R, Greil R, et al. Bevacizumab continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab + chemotherapy: Biomarker findings from ML18147. Am Soc of Clin Oncol Gastrointestinal Cancers Symposium. January 2013, Poster 452.

Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007;12:601-9.

Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg. 2003;90:205-14.

Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006;66:3992-5.

Liu LX, Zhang WH, Jiang HC. Current treatment for liver metastases from colorectal cancer. World J Gastroenterol. 2003;9:193–200.

Liu Y, Starr MD, Bulusu A, et al. Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab . Cancer Med. 2013;2:234–42.

Lothe RA, Peltomäki P, Meling GI, et al. Genomic instability in colorectal cancer: relationship to clinicopathological variables and family history. Cancer Res. 1993;53:5849-52.

Loupakis F, Cremolini C, Fioravanti A, et al. Pharmacodynamic and pharmacogenetic angiogenesis-related markers of first-line FOLFOXIRI plus bevacizumab schedule in metastatic colorectal cancer. Br J Cancer. 2011;104:1262-9.

Lyman GH, Khorana AA, Falanga A. American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol. 2007;25:5490–505.

Maisonpierre PC, Suri C, Jones PF, et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Science. 1997; 277:55-60.

Mandala M, Mosconi S, Quadri A et al. Neoadjuvant chemotherapy for patients with liver metastases from colorectal cancer. Expert Rev Anticancer Ther. 2007;7:887–97.

Mathijssen R, de Jong F, Loos W et al. Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults: Does It Make a Difference? The Oncologist 2007; 12:913–923.

Mazzieri R, Pucci F, Moi D et al. Targeting the ANG2/TIE2 Axis Inhibits Tumor Growth and Metastasis by Impairing Angiogenesis and Disabling Rebounds of Proangiogenic Myeloid Cells. Cancer Cell 2011; 19:512–526.

Meadows KL, Hurwitz HI. Anti-VEGF therapies in the clinic. Cold Spring Harb Perspect Med. 2012;2: a006577.

Mita AC, Takimoto CH, Mita M, et al. Phase 1 study of AMG 386, a selective angiopoietin 1/2-neutralizing peptibody, in combination with chemotherapy in adults with advanced solid tumors. Clin Cancer Res 2010; 16:3044-56.

Mohile S, Hardt M, Tew W et al. Toxicity of Bevacizumab in Combination with Chemotherapy in Older Patients. The Oncologist 2013, 18:408-414.

Mook OR, Frederiks WM, Van Noorden CJ. The role of gelatinases in colorectal cancer progression and metastasis. Biochim Biophys Acta. 2004;1705(2):69-89.

Nagy J and Dvorak H. Heterogeneity of the tumor vasculature: the need for new tumor blood vessel type-specific targets. Clin Exp Metastasis 2012; 29:657–662.

National Cancer Institute. http://www.cancer.gov/cancertopics/types/colon-and-rectal. Accessed on 5 Jan 2014.

Noonan S, Martin P, Biniecka A, et al. Correlation of high levels of immature blood vessels in colorectal tumors with longer survival following bevacizumab treatment. J Clin Oncol 29:2011(Suppl); Abstract 10586.

Ochiumi T, Tanaka S, Oka S, et al. Clinical significance of angiopoietin-2 expression at the deepest invasive tumor site of advanced colorectal carcinoma. Int J Oncol. 2004;24:539-47.

Pagès F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med. 2005;353:2654-66.

Pancione M, Forte N, Sabatino L, et al. Reduced beta-catenin and peroxisome proliferator-activated receptor-gamma expression levels are associated with colorectal cancer metastatic progression: correlation with tumor-associated macrophages, cyclooxygenase 2, and patient outcome. Hum Pathol. 2009;40:714-25.

Pantel K, Alix-Panabières C. Real-time liquid biopsy in cancer patients: fact or fiction? Cancer Res. 2013;73:6384-8.

Peeters M, Strickland AH, Lichinitser M, et al. A randomised, double-blind, placebo-controlled phase 2 study of trebananib (AMG 386) in combination with FOLFIRI in patients with previously treated metastatic colorectal carcinoma. Br J Cancer. 2013;108:503–11.

Penna C, Nordlinger B. Colorectal metastases (liver and lung). Surg Clin North Am. 2002;82:1075–90.

Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23:609-18.

Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of Epoetin and Darbepoetin in adults patients with cancer. J Clin Oncol. 2010: 28:4996–5010.

Roy R, Yang J, Moses MA. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. J Clin Oncol. 2009;27:5287-97.

Rubatt JM, Darcy KM, Hutson A, et al. Independent prognostic relevance of microvessel density in advanced epithelial ovarian cancer and associations between CD31, CD105, p53 status, and angiogenic marker expression: A Gynecologic Oncology Group study. Gynecol. Oncol. 2009; 112:469-74.

Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–9.

Samuels Y, Ericson K. Oncogenic PI3K and its role in cancer. Curr Opin Oncol. 2006;18:77-82.

Schaefer W, Regula JT, Bähner M, et al. Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies. Proc Natl Acad Sci USA. 2011;108:11187–92.

Scharpfenecker M, Fiedler U, Reiss Y, et al. The Tie-2 ligand angiopoietin-2 destabilizes quiescent endothelium through an internal autocrine loop mechanism. J Cell Sci. 2005;118:771-80.

Sfiligoi C, de Luca A, Cascone I, et al. Angiopoietin-2 expression in breast cancer correlates with lymph node invasion and short survival. Int J Cancer. 2003;103:466-74.

Simons CC, Hughes LA, Smits KM, et al. A novel classification of colorectal tumors based on microsatellite instability, the CpG island methylator phenotype and chromosomal instability: implications for prognosis. Ann Oncol. 2013;24:2048-56.

Smith TJ, Khatcheressian J, Ozer H, et al. Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24:3187–205.

Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, Bevacizumab, and Mitomycin in First-Line Treatment of Metastatic Colorectal Cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol. 2010;28:3191–98.

Tol J, Dijkstra JR, Klomp M, et al. Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab. Eur J Cancer. 2010;46:1997-2009.

Van Cutsem E, Nordlinger B and Cervantes A. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Annals of Oncology 2010; 21: 93–97.

Vibert E, Canedo L, Adam R. Strategies to treat primary unresectable colorectal liver metastases. Semin Oncol. 2005;32(6 Suppl 8):33–9.

Volkova E, Willis JA, Wells JE, et al. Association of angiopoietin-2, C-reactive protein and markers of obesity and insulin resistance with survival outcome in colorectal cancer. Br J Cancer. 2011;104:51-9.

Wang T and Lockhart A. Aflibercept in the Treatment of Metastatic Colorectal Cancer. Clinical Medicine Insights: Oncology 2012; 6: 19–30.

Wang D, Zhang S, Zhao H et al. Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. J Clin Pharmacol 2009; 49:1012-1024.

Wedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol. 2006;24:769-77.

Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med. 2004;10:145-7.

Willett CG, Boucher Y, Duda DG, et al. Surrogate markers for angiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients. J Clin Oncol. 2005;23:8136-39.

Xin Y, Li J, Wu J, Kinard R, Weekes CD, et al. Pharmacokinetic and pharmacodynamics analysis of circulating biomarkers of anti-NRP1, a novel antiangiogenesis agent, in two phase I trials in patients with advanced solid tumors. Clin Cancer Res. 2012;18:6040-8.

Yoshiji H, Kuriyama S, Noguchi R, et al. Angiopoietin 2 displays a vascular endothelial growth factor dependent synergistic effect in hepatocellular carcinoma development in mice. Gut. 2005;54:1768-75.

Zhou Q, Peng RQ, Wu XJ, et al. The density of macrophages in the invasive front is inversely correlated to liver metastasis in colon cancer. J Transl Med. 2010;8:13.

Zhu AX, Sahani DV, Duda DG et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol. 2009; 27(18):3027-3.

Appendix 1 Schedule of Assessments

	Screening / Baseline		Treatment Cycle (14 days)											DP Visit	EoS Visit [a]	Post Study Visit [b]	Survival Status Follow up [c]
			1		2	3	4	5	6-8	9	10-12	13	≥14				
Day	**-28 to -1**	**-7 to -1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
RO5520985 or bevacizumab			X		X	X	X	X	X	X	X	X	X				
mFOLFOX-6 Administration (Induction therapy for up to 8 Cycles)			X		X	X	X	X	X								
5-FU/folinic acid (Maintenance therapy for up to 24 months)										X [d]	X	X	X				
Written Informed Consent [e]	X																
Medical/Cancer History	X																
Demographics and Body Height	X																
Archival Primary Tumor Tissue			X (to be provided within first 4 weeks of treatment)														
Serum/Urine Pregnancy Test		X															
12-lead ECG [f]	X		X			X									X		
TTE or MUGA	X														X		
Physical Exam. and Body Weight [g]	X		X [h]		X	X	X	X	X	X	X	X	X		X		
Hematology/Biochem./Coagulation [g]	X		X [h]		X	X	X	X	X	X	X	X	X		X		
Vital Signs [i]	X		X [h]		X	X	X	X	X	X	X	X	X		X		
ECOG Performance Status [g]	X		X [h]		X	X	X	X	X	X	X	X	X		X		
Urinalysis (dipstick for proteinuria) [g,j]	X		X [h]		X	X	X	X	X	X	X	X	X		X		
RECIST Tumor Assessment [k]	X							X		**X**		X			X		X
Tumor marker every 2nd cycle (CEA)	X					X		X	X [o]	X	X [o]	X		X	X		
Plasma samples for Biomarkers [l, m] Part II			X	X				X		X		X		X	X		
Plasma for MMP-2 and MMP-9 [l] - Part II			X											**X**	**X**		
Plasma for circulating tumor DNA [l] Part II			X					X		X		X		X	X		
RCR – Plasma - Part II			X														
RCR – Blood for DNA isolation - Part II			X														
HAHA [n]			X					X		X		X			X	X (opt)	

Appendix 1 Schedule of Assessments (cont.)

	Screening / Baseline		Treatment Cycle (14 days)										DP Visit	EoS Visit [a]	Post Study Visit [b]	Survival Status Follow up [c]
			1		2	3	4	5	6-8	9	10-12	13	≥14				
Day	**-28 to -1**	**-7 to -1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**				
AEs and Concomitant Medication	Continuously monitored. Prior first study drug administration only SAEs related to protocol mandated procedures to be reported. For AE and SAE reporting period refer to Section 5.3.1.															
PK blood samples	Refer to separate PK tables in Appendix 2 and Appendix 3															
Plasma samples for Ang-2	Refer to separate PK table in Appendix 2															

AE = adverse event; DP = disease progression; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoS = end of study; HAHA = human anti-human ant body; MUGA = multigated acquisition scan; PK = pharmacokinetic; RCR = Roche Clinical Repository; SAE = serious adverse event; TTE = two dimensional transthoracic echocardiography.

*NOTE: All assessments on dosing days need to be performed **prior to dosing** except otherwise specified.*

[a] End of Study Visit to occur within 5 (± 1) weeks after discontinuing study drug treatment.

[b] Post Study Visit to occur 2 months (±14 days) after last dose of treatment.

[c] Survival Status Follow up Visits approximately every 3 months after EoS Visit until death, loss to follow-up, or study termination by Roche, whichever occurs first.

[d] After induction therapy has been completed, maintenance treatment will start at the following cycle; however, latest from Cycle 9 onwards, for a maximum of 24 months.

[e] Informed consent must be obtained prior to any study-related procedures.

[f] 12-lead ECG: In triplicates with 2–5 minutes between readings. ECG during treatment needs to be performed 4 (±2) hrs after end of infusion

[g] Pre-infusion assessments of hematology, biochemistry, coagulation, urinalysis, physical examination/body weight, and ECOG: time window of -3 days.

[h] If certain screening assessments are performed one day prior to the 1st administration of study drug, the assessments do not have to be repeated on Day 1 Cycle 1.

[i] Vital signs: On infusion days: Predose, at end of infusion, 1 hr (±15 min) , 2 hrs (±30 min) and 4 hrs (±1.5 hr) after end of infusion. For patients who discontinue treatment with RO5520985/bevacizumab but continue with chemotherapy the frequency of the vital signs assessment can be reduced as follows: pre-infusion and either at end of infusion or at 1hr (±15 min) post infusion.

[j] Urinalysis (urine dipstick for proteinuria): 24-hrs urine protein analysis in ≥2+ dipstick reading (with result available prior next dosing).

[k] RECIST tumor assessment: Performed every 8 weeks (±7 days). Results of tumor assessments using CT/MRI prior to obtaining informed consent and within 28 days prior to Day 1 may be used; If patient is discontinued from treatment for any reason other than progression, an end of study CT/MRI is to be performed only if it has not been done ≤28 days prior to this day. IPatients with previously documented tumor progression will not require additional tumor-reassessment by CT/MRI at End of Study visit. **If a patient discontinues therapy for reasons other than progression, the patient will be followed by regular CT assessments according to institutional standard of care until documentation of progressive disease, initiation of another anticancer therapy (including secondary resection), withdrawal of consent, or death.** Optional radiology report from latest pre-study CT scan not older than 12 weeks prior to C1D1 should be provided for assessment of tumor growth kinetics within 6 weeks of patient entering the study.

[l] Plasma samples for biomarkers, MMP-2, MMP-9 and circulating tumor DNA: Samples at DP visit should be drawn within 1 week after imaging shows DP. In case EoS Visit overlaps with DP Visit only one sample needs to be drawn. For patients who discontinue RO5520985/bevacizumab but continue with chemotherapy the assessments can be skipped .

[m] Additional 2 mL EDTA plasma will be collected at baseline prior dosing.

[n] HAHA additional sample to be taken in case of NCI CTC-AE ≥ Grade3 IRR. In case a patient discontinues RO5520985/bevacizumab but continues with chemotherapy the assessment at EOS Visit can be skipped.

[o] Blood Tumor marker (CEA) to be assessed baseline and every 2nd Cycle under treatment, i.e. C3, C5, C7, C9, C11, C13, C15, etc.

Appendix 2 Schedule of Pharmacokinetic Assessments for RO5520985

(Part I)

Cycle	Day	Time from start of infusion (h)	PK Sampling
Cycle 1	1	Predose	X
		End of Infusion	X
		1 (± 0.25)	X
		2 (± 0.25)	X
		4 (± 1)	X
	2	24 (± 4)	X
	4	72 (± 24)	X [a]
	6	120 (± 24)	X [a]
	8	168 (± 24)	X [a]
Cycle 2 – Cycle 5	1	Pre-dose	X
		End of Infusion	X
Cycle **6**	1	Pre-dose	X
		End of Infusion	X
		1 (± 0.25)	X
		2 (± 0.25)	X
		4 (± 1)	X
	2	24 (± 4)	X
	4	72 (± 24)	X [a]
	6	120 (± 24)	X [a]
	8	168 (± 24)	X
Cycle 7-8	1	Pre-dose	X
		End of Infusion	X
Disease progression [b]			X
End of Study Visit			X

PK = pharmacokinetic.

[a] In Cycle 1, only one of the PK samples to be taken on Day 4, Day 6 and Day 8 is mandatory and can be chosen at the investigators discretion. In Cycle 6 one of the samples to be taken on D4 and D6 can be skipped at investigators discretion

[b] Unscheduled PK samples will be taken at the time of disease progression (samples at DP Visit should be drawn within 1 week after imaging shows disease progression). In case DP Visit overlaps with EoS Visit, only the EoS Visit sample should be drawn.

Appendix 2 Schedule of Pharmacokinetic Assessments for RO5520985 (cont.)

(Part II)

Cycle	Day	Time from start of infusion (h)	PK Sampling[d]
Cycle 1	1	Predose	X
		End of Infusion	X
		1 (± 0.25)	X
		2 (± 0.25)	X
		4 (± 1)	X[c]
	2	24 (± 4)	X
	4	72 (± 24)	X[a]
	6	120 (± 24)	X[a]
	8	168 (± 24)	X[a]
Cycle 2 – Cycle 7	1	Pre-dose	X
		End of Infusion	X
Cycle 8	1	Pre-dose	X
		End of Infusion	X
		1 (± 0.25)	X
		2 (± 0.25)	X
		4 (± 1)	X[c]
	2	24 (± 4)	X[c]
	4	72 (± 24)	X[a]
	6	120 (± 24)	X[a]
	8	168 (± 24)	X
Disease progression[b]			X
End of Study Visit			X

PK = pharmacokinetic.

[a] In Cycle 1, only one of the PK samples to be taken on Day 4, Day 6 and Day 8 is mandatory and can be chosen at the investigators discretion. In Cycle 8, one of the samples to be taken on D4 and D6 can be skipped at investigators discretion

[b] Unscheduled PK samples will be taken at the time of disease progression (samples at DP Visit should be drawn within 1 week after imaging shows disease progression. In case DP Visit overlaps with EoS Visit, only the EoS Visit sample should be drawn.

[c] An additional blood sample will be drawn for measurement of Ang-2 (free and total). The assessment can be skipped for patients who discontinue treatment with RO5520985/bevacizumab but continue with chemotherapy.

[d] For patients who discontinue treatment with RO5520985/bevacizumab but continue with chemotherapy the PK assessments can be skipped.

Appendix 3 Schedule of Pharmacokinetic Assessments for FOLFOX Components (Part I only)

Cycle	Day	Time from start of infusion of each individual agent	Oxaliplatin	5-FU bolus
Cycle 1	1	Predose	X	X
		End of bolus 5-FU		X
		30 minutes	X	
		1 hour	X	X
		2 hours	X	
		2,5 hours	X	
		3 hours	X	X
		4 hours	X	
	2	24 hours	X	
Cycle 6	1	Predose	X	X
		End of bolus 5-FU		X
		30 minutes	X	
		1 hour	X	X
		2 hours	X	
		2,5 hours	X	
		3 hours	X	X
		4 hours	X	
	2	24 hours	X	

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

mFOLFOX-6 will be administered as follows after Infusion of RO5520985/ bevacizumab:

1. Oxaliplatin 85 mg/m^2 IV concurrently (using a y connector) with folinic acid 400 mg/m^2 IV (or 200 mg/m^2 I-isomer form) over 120 minutes
2. 5-FU 400 mg/m^2 administered as an IV bolus
3. 5-FU 2400 mg/m2, continuous IV infusion over 46 +/- 2 hours

Appendix 4
Cockcroft–Gault Formula

Creatinine Clearance (mL/min) for Males

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]})}{(72 \times \text{serum creatinine [mg/dL]})}$$

Creatinine Clearance (mL/min) for Females

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]} \times \text{body weight [kg]})}{(72 \times \text{serum creatinine [mg/dL]})} \times 0.85$$

Appendix 5 ECOG Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

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

ECOG = Eastern Cooperative Oncology Group.

[a] As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982.

Appendix 6 NYHA Classification

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co. 1994:253–256.

Appendix 7 ICH Guidelines – Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- Is fatal; [results in death] [NOTE: death is an outcome, not an event]
- Is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- Required in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For Serious Adverse Events, causality can be one of 2 possibilities:

- No (unrelated; equals not drug related).
- Yes (remotely, possibly, probably or definitely drug related).

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Appendix 7 ICH Guidelines – Topic E2 (cont.)

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period (protocol section 5.3.1), if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

Appendix 8 RECIST Criteria, Version 1.1

(excerpt from original publication)

Measurability of tumor at baseline

De nitions

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

Measurable Tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also below 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable Tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, in ammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identi ed by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain lms are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to con rm the presence or disappearance of 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 or MRI can be considered as measurable lesions if the soft tissue component meets the de nition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically de ned simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by de nition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the de nition of measurability described above. However, if non-cystic lesions are present in the same patient, 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

Speci cations by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identi ed and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are super cial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly de ned and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has de ned measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

If prior to enrolment it is known that a patient 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 (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identi ed by ultrasound in the course of the study, con rmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to con rm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease speci c, instructions for their measurement should be incorporated into protocols on a disease speci c basis. Speci c guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in rst-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological con rmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is de ned by the presence of at least one measurable lesion (as detailed above). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a xed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of ve lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identi ed as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10mm by CT scan).

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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 de ned as measurable and may be identi ed 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; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and quali es 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 the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum 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 to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identi ed as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria

This section provides the de nitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *Complete Response (CR):* 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 (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identi ed 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 complete response criteria are met, since a normal lymph node is de ned as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

***Target lesions* that become *'too small to measure'*:** while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is 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 and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a de nable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the de nitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points speci ed in the protocol.

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

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in 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.

When the patient has only non-measurable disease: this circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quanti ed (by de nition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no speci c criteria for the identi cation of new radiographic lesions; however, the nding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or ndings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or are of pre-existing lesions).

This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identi ed 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 patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans con rm there is de nitely a new lesion, then progression should be declared using the date of the initial scan.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identi ed according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease con rmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not con rmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for con rmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the ndings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Furthermore, depending on the nature of the study and the protocol requirements, it may also require con rmatory measurement. Speci cally, in non-randomised trials where response is the primary endpoint, con rmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol speci ed time point, a response assessment occurs. Table 1 below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be “Unable to Assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as ‘not assessed’, the response for non-target lesions should be “Unable to Assess” (except where there is clear progression). Overall response would be “Unable to Assess” if the target response is “Unable to Assess” (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best overall response: all time points

The *best overall response* will be determined by statistical programming once all the data for the patient is known.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Table 1 Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

Table 3 Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (eCRF).

In trials where con rmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a con rmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that de ne 'early progression, early death and non-evaluability' are study speci c and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

Appendix 8 RECIST Criteria, Version 1.1 (cont.)

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (ne needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent brosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease speci c medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal ndings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is con rmed, the date of progression should be the earlier date when progression was suspected.