

CLINICAL STUDY PROTOCOL

PRODUCT: BAX69 (Imalumab)

STUDY TITLE: A Phase 2a Randomized, Open-Label Study to Assess the Safety, Tolerability, and Efficacy of BAX69 in Combination with 5-FU/Leucovorin or Panitumumab versus Standard of Care in Subjects with Metastatic Colorectal Cancer

STUDY SHORT TITLE: Phase 2a Study of BAX69 and 5-FU/Leucovorin or Panitumumab versus Standard of Care in Subjects with Metastatic Colorectal Cancer

PROTOCOL IDENTIFIER: 391401

CLINICAL TRIAL PHASE 2a

AMENDMENT 5 (GLOBAL): 2016 MAY 09

Replaces:

AMENDMENT 2 (GLOBAL): 2015 JUL 13

ALL VERSIONS:

Amendment 4 (Germany Version): 2015 DEC 16

Amendment 3 (United Kingdom [UK] Version): 2015 OCT 02

Amendment 2 (GLOBAL): 2015 JUL 13

Amendment 1 (GLOBAL): 2015 MAR 06

Original (GLOBAL): 2014 DEC 10

OTHER ID(s)

EudraCT Number: 2015-000896-28

IND NUMBER: 112850

Study Sponsor(s):	Baxalta US Inc. One Baxter Way Westlake Village, CA 91362 USA	Baxalta Innovations GmbH Industriestrasse 67 A-1221 Vienna AUSTRIA
--------------------------	---	--

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

PPD [REDACTED], MD
PPD [REDACTED] Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs), including suspected unexpected serious adverse reactions (SUSARs), to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (eCRF) WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE eCRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.

Drug Safety contact information: see SAER Form.

Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, see the following:

- Adverse events (AEs), Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

Serious adverse event report contact information by country:

Country	Telephone	Fax
Germany	PPD	PPD
Spain	PPD	PPD
United Kingdom	PPD	PPD
United States	PPD	PPD

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX69 (imalumab), a fully human recombinant anti-oxidized macrophage migration inhibitory factor (anti-oxMIF) antibody
Name(s) of Active Ingredient(s)	BAX69 (imalumab)
CLINICAL CONDITION(S)/INDICATION(S)	
Metastatic colorectal cancer (mCRC)	
PROTOCOL ID	391401
PROTOCOL TITLE	A Phase 2a Randomized, Open-Label Study to Assess the Safety, Tolerability, and Efficacy of BAX69 in Combination with 5-FU/Leucovorin or Panitumumab versus Standard of Care in Subjects with Metastatic Colorectal Cancer
Short Title	Phase 2a Study of BAX69 and 5-FU/Leucovorin or Panitumumab versus Standard of Care in Subjects with Metastatic Colorectal Cancer
STUDY PHASE	Ph2a
PLANNED STUDY PERIOD	
Initiation	Q2 2015
Primary Completion	Q4 2016
Study Completion	Estimated study completion will occur when 75% of overall survival (OS) events are reported.
Duration	Approximately 21 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose The purpose of this study, in subjects with progressive measurable mCRC, is as follows: <ul style="list-style-type: none">• To evaluate the safety and tolerability of imalumab in combination with 5-fluorouracil (5-FU)/leucovorin (LV) or panitumumab to determine the recommended phase 2 dose (RP2D) of each combination• To compare the efficacy of imalumab in combination with 5-FU/LV versus standard of care (SoC) (investigator choice) as third or fourth treatment line in subjects with KRAS mutated (mut) and/or NRAS mut tumors• To compare the efficacy of imalumab in combination with panitumumab versus SoC (investigator choice) as third or fourth treatment line in subjects with KRAS wild type (wt) and NRAS wt tumors Furthermore, the pharmacokinetic (PK) profile of imalumab in combination with 5-FU/LV or panitumumab will be characterized, and limited pharmacodynamic (PD) serum markers will be explored.	
Primary Objectives <ol style="list-style-type: none">1. To determine the RP2D of imalumab in combination with 5-FU/LV or panitumumab (Part 1)2. To compare progression-free survival (PFS) between imalumab in combination with 5-FU/LV for subjects with KRAS mut and/or NRAS mut tumors or in combination with panitumumab for subjects with KRAS wt and NRAS wt tumors, versus SoC (investigator choice) as third or fourth treatment line (Part 2)	

Secondary Objectives	
<ol style="list-style-type: none">1. To compare overall response rate (ORR) and clinical benefit rate (CBR) in subjects treated at RP2D with imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line2. To compare overall survival (OS) of subjects who received imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line3. To assess the safety and tolerability of imalumab in combination with 5-FU/LV or panitumumab4. To characterize the PK of imalumab in combination with 5-FU/LV or panitumumab5. To compare quality of life (QoL) of subjects who received imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line	
Exploratory Objectives	
<ol style="list-style-type: none">1. To characterize oxidized macrophage migration inhibitory factor (oxMIF) and total macrophage migration inhibitory factor (MIF) in plasma prior to and during treatment with imalumab in combination with 5-FU/LV or panitumumab2. To characterize tumor-associated genetic alterations in blood/urine (for all subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for exploratory biomarker analyses)3. To compare disease-specific QoL and health utility in subjects treated with imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Interventional; 2-treatment-arm; randomized Safety; Tolerability; PK; Exploratory Efficacy and Exploratory PD
Control Type	SoC (including best supportive care) per investigator's choice (Part 2)
Study Indication Type	Treatment of mCRC in third or fourth line
Intervention model	Part 1: Safety Run-in Part 2: Randomized, controlled, parallel, 2-treatment-arm
Blinding/Masking	Open-label
Study Design	<p>This Phase 2a study will be conducted in approximately 40 study sites in the United States (US) and the European Union (EU). The study will comprise 2 sequential parts (subjects can only participate in either Part 1 or Part 2 of the study):</p> <ul style="list-style-type: none">• Part 1: A Safety Run-in period to evaluate 2 predefined doses (7.5 mg/kg and 10 mg/kg) of imalumab given every week (QW) in combination with infusional 5-FU/LV given every 2 weeks (Q2W) in subjects with mutated tumors (KRAS mut, and/or NRAS mut), or imalumab in combination with panitumumab given Q2W in subjects with wild type tumors (KRAS wt and NRAS wt). Prior to entry into the study, subjects will be stratified according to their KRAS/NRAS mutation status. Treatments will be administered in 4-week (28-day) cycles.

	<ul style="list-style-type: none">Part 2: A 2-treatment-arm design using a 2:1 ratio for subjects to receive imalumab + 5-FU/LV or imalumab + panitumumab (Arm A) or SoC per investigator choice (Arm B). Prior to randomization, subjects will be stratified according to their mutation status. Within each stratum, subjects will be randomized in a 2:1 ratio to receive imalumab + 5-FU/LV (KRAS mut and/or NRAS mut tumors) or imalumab + panitumumab (KRAS wt and NRAS wt tumors) (Arm A) or SoC per investigator choice (Arm B). <p>For all subjects in Parts 1 and 2, treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent.</p> <p>Part 1: Safety Run-in</p> <p>For each combination, subjects will be enrolled into 2 sequential cohorts, with a minimum of 3 and a maximum of 6 subjects per cohort.</p> <p>For each combination, enrollment will proceed according to the following rules based on the occurrence of dose-limiting toxicities (DLTs):</p> <ul style="list-style-type: none">If zero out of 3 evaluable subjects experience a DLT during the first 28 days after the first administration of study drug at the first dose level, the second dose level will be opened for enrollment after review of the safety data by the Data Review Committee (DRC).If 1 out of 3 evaluable subjects experiences a DLT during the first 28 days after administration of study drug at the first dose level, 3 additional subjects will be enrolled at the first dose level, for a total of 6 evaluable subjects. After review of the safety data of all 6 evaluable subjects, the DRC will decide if the second dose level or a lower dose level will be explored.If 2 or more evaluable subjects experience a DLT during the first 28 days after the first administration of study drug at the first dose level, the second dose level <u>will not</u> be open to enrollment and the DRC will decide if a lower dose level will be explored. <p>The DRC will meet for safety reviews after 3 subjects in a dosing cohort have completed the first treatment cycle. The DRC will decide either to enroll additional subjects or open the next dose level. For each combination, based on all data of all evaluable subjects, the DRC will either determine the RP2D, or will decide to explore an intermediate dose level.</p> <p>DLT Definition</p> <p>A DLT is defined as any drug-related treatment-emergent adverse event (TEAE) (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) that occurs during the first 28 days after treatment start and that meets any of the following criteria:</p> <ul style="list-style-type: none">Any \geq Grade 3 non-hematologic toxicity excluding:<ol style="list-style-type: none">Mucositis/stomatitis of Grade 3 that resolves to Grade 1 or less with supportive measures within 7 daysDiarrhea of < 3 days duration following adequate and optimal therapyNausea and vomiting of < 3 days duration with adequate and optimal therapy
--	--

	<ul style="list-style-type: none">d. Fatigue of < 7 days duration following initiation of adequate supportive caree. Alopeciaf. Any single laboratory value out of the normal range that has no clinical significance and that resolves to \leq Grade 2 with adequate measures within 7 days; transient Grade 3 elevations (lasting < 5 days) of hepatic transaminases in the absence of simultaneous increase in serum bilirubin• Any Grade 4 hematologic toxicity excluding:<ul style="list-style-type: none">a. Grade 4 neutropenia lasting for \leq 5 days and not accompanied by feverb. Isolated Grade 4 lymphocytopenia without clinical correlate• Grade 3 febrile neutropenia• Grade 3 thrombocytopenia associated with bleeding• Any life-threatening complication or abnormality not covered in the NCI CTCAE v4.03
--	---

Determination of RP2D

For each combination, based on all data of all evaluable subjects, the DRC will determine the RP2D, or decide if an intermediate dose level must be explored.

Part 2: Exploratory Phase 2a

This is a 2-treatment-arm phase using a 2:1 ratio for subjects to receive imalumab + 5-FU/LV or imalumab + panitumumab (Arm A) or SoC per investigator choice (Arm B). Prior to randomization, subjects will be stratified according to their KRAS/NRAS status. Within each stratum, subjects will be randomized in a 2:1 ratio to receive imalumab + 5-FU/LV (KRAS mut and/or NRAS mut tumors) or imalumab + panitumumab (KRAS wt and NRAS wt tumors) (Arm A) or SoC per investigator choice (Arm B). Randomization will occur via an Interactive Response Technology (IRT) System. For each combination in Arm A, subjects will receive imalumab at the RP2D determined in Part 1 for the corresponding combination. All subjects will be treated until disease progression, unacceptable toxicity, or withdrawal of consent. An independent Data Safety Monitoring Board (DSMB) comprised of recognized experts in the field of oncology and biostatistics clinical care and research, will review accumulating unblinded safety data of subjects in Part 2 on a quarterly basis. The composition, activities, and responsibilities of the DSMB are described in further detail in the DSMB Charter.

	<p><u>Assessments</u></p> <p>Safety data will be regularly monitored throughout the study. The investigator will evaluate the study treatment antitumor activity after completion of every other treatment cycle (ie, every 2 cycles) using magnetic resonance imaging (MRI) or computerized tomography (CT) imaging and in accordance to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in all subjects treated at RP2D. In Part 1, and in Arm A of Part 2, plasma levels of imalumab, oxMIF, and total MIF will be measured. The effect of imalumab in combination with 5-FU/LV or panitumumab on tumor-associated genetic biomarkers will be monitored. Blood and urine samples will be collected from those subjects who provide consent for this optional exploratory analysis. It is possible that blood/urine biomarkers may correlate with clinical outcome (safety and efficacy) in response to imalumab treatment.</p>
Planned Duration of Subject Participation	<p>Subject participation includes a maximum of 4 weeks for screening, and 30 (± 7) days for post-treatment safety follow-up. Subjects will receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Subjects will be followed until progression is clinically or radiologically documented.</p> <p>The duration of the study is estimated as a total of 21 months, inclusive of approximately 15 months to complete accrual, followed by approximately 6 months for primary outcome measure. Study completion is estimated to occur when 75% of OS events have been reported.</p>
Primary Safety Outcome Measure	<ul style="list-style-type: none">Occurrence of DLTs (Part 1)
Primary Efficacy Outcome Measure	<ul style="list-style-type: none">PFS, defined as time between treatment initiation and tumor progression (per RECIST v1.1) or death from any cause, with censoring of subjects who are lost to follow-up or withdraw consent (Part 2)
Secondary Outcome Measures	
Immunogenicity:	<ul style="list-style-type: none">Occurrence of binding and/or neutralizing anti-imalumab antibodiesIncidence and severity of infusion reactions after imalumab
Safety:	<ul style="list-style-type: none">Occurrence of TEAEs and/or serious adverse events (SAEs), regardless of causality or relationship to study drug, using NCI CTCAE v4.03Other safety measurements: physical or instrumental examinations, electrocardiograms (ECGs), vital signs, clinically relevant changes in instrumental examinations or laboratory values
Efficacy:	<ul style="list-style-type: none">Response evaluation according to RECIST v1.1OS time from randomization to death of any cause

PK: <ul style="list-style-type: none">Imalumab plasma PK will be characterized using a population PK modeling approach, in combination with PK data from other studies.
QoL: <ul style="list-style-type: none">Quality of life assessed using the EORTC QLQ-C30
Exploratory Outcome Measures
PD: <ul style="list-style-type: none">Levels of oxMIF and total MIF in plasma
Genetic biomarkers: <ul style="list-style-type: none">Tumor-associated genetic alterations in blood/urine (for subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for exploratory biomarker analyses)
The sponsor will obtain available historical tumor mutational testing results for subjects.
QoL: <ul style="list-style-type: none">Quality of life assessed using the EORTC QLQ-CR29European Quality of Life – 5 Dimensions (EQ-5D)
INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION
Active Products in Experimental Arms Imalumab Dosage form: solution, vial for infusion Dosage frequency: QW over 4-week cycles Mode of Administration: IV with a flow rate of 1.0 mL/min to 3.6 mL/min Doses in Part 1: 7.5 mg/kg and 10 mg/kg Dose in Part 2: For each combination, the dose will be the RP2D as determined during Part 1 Panitumumab Dosage frequency: Q2W Mode of Administration: IV over 60 minutes (maximum 1000 mg; if > 1000 mg, infuse over 90 minutes) Dose (Parts 1 and 2): 6 mg/kg In case of mild-moderate infusion reaction, reduce infusion rate by 50%. In case of a severe infusion reaction, the infusion must be immediately stopped and panitumumab permanently discontinued. 5-FU/LV Dosage frequency: Q2W Mode of Administration: IV over 48 hours Dose (Parts 1 and 2): LV 400 mg/m ² over 2 hours, followed by 5-FU 2400 mg/m ² IV over 46 hours
Control Drugs Investigator's choice (including best supportive care) will be done according to local SoC

SUBJECT SELECTION	
Targeted Accrual	Part 1: 12 to 24 subjects; non-evaluable subjects will be replaced to meet study objectives. Part 2: Maximum of 66 subjects
Number of Groups/Arms/Cohorts	Part 1: 2 cohorts per combination Part 2: 2 treatment arms
Inclusion Criteria	
Subjects must meet ALL of the following criteria to be eligible for this study:	
<ol style="list-style-type: none">1. Provision of a signed informed consent2. Male and female subjects 18 years of age and older at the time of screening3. Subjects who progressed after receiving at least 2, but no more than 3, prior cancer drug therapy treatment lines including SoC in the metastatic setting4. Anticipated life expectancy > 3 months at the time of screening5. Weight between 40 kg and 180 kg6. Histologically or cytologically confirmed diagnosis of CRC7. Metastatic CRC not amenable to surgical resection8. Known KRAS, NRAS mutation status (if unknown status for either of these genes, and no archival tissue is available, a fresh tumor biopsy will be obtained)9. At least 1 measurable lesion as defined by RECIST v1.110. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-211. Adequate hematological function, defined as:<ol style="list-style-type: none">a. Platelet count \geq 100,000/μLb. Prothrombin time and activated partial thromboplastin time (aPTT) $<$ 1.5 times the upper limit of normal (ULN)c. Absolute neutrophil count (ANC) \geq 1,000/μLd. Hemoglobin \geq 9 g/dL, without the need for transfusion in the 2 weeks prior to screening12. Adequate renal function, defined as serum creatinine \leq 2.0 times ULN and creatinine clearance $>$ 50 mL/min or estimated glomerular filtration rate $>$ 50ml/min/1.73 m²13. Adequate liver function, defined as:<ol style="list-style-type: none">a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) \leq 2.5 times ULN for subjects without liver metastases, or \leq 5 times ULN in the presence of liver metastasesb. Bilirubin \leq 2.0 times ULN, unless subject has known Gilbert's syndrome14. Adequate venous access15. For female subjects of childbearing potential, the subject presents with a negative serum pregnancy test at screening and agrees to employ 2 forms of adequate birth control methods, including at least 1 barrier method (eg, diaphragm with spermicidal jelly or foam, or [for male partner] condom) throughout the course of the study and for at least 90 days after the last administration of imalumab. In addition, these birth control methods must be continued for at least 180 days after last administration of 5-FU in subjects who receive this treatment. Secondary contraceptive measures could be either birth control pills, patches, or intrauterine devices	

<p>16. For male subjects, they must agree to use adequate contraceptive measures including at least 1 barrier method (eg, condom with spermicidal jelly or foam and [for the female partner] diaphragm with spermicidal jelly or foam, birth control pills/patches, or intrauterine device) and abstain from sperm donation throughout the course of the study and for at least 90 days after the last administration of imalumab. In addition, these birth control methods must be continued for at least 180 days after last administration of 5-FU in subjects who receive this treatment</p> <p>17. Subject is willing and able to comply with the requirements of the protocol</p>

Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for the study:

- 1. Known central nervous system metastases
- 2. Prior malignancy(s) within the past 3 years, with the exception of curatively treated basal or squamous cell carcinoma of the skin, locally advanced prostate cancer, ductal carcinoma in situ of breast, in situ cervical carcinoma and superficial bladder cancer
- 3. Prior treatment with panitumumab for subjects with KRAS wt and NRAS wt tumors
- 4. Known history of keratitis, ulcerative keratitis, or severe dry eye in subjects with KRAS wt and NRAS wt tumors
- 5. Residual adverse event (AE) from previous treatment > Grade 1, except neuropathy and alopecia
- 6. Prior intolerance to fluoropyrimidine for subjects with KRAS mut and/or NRAS mut tumors
- 7. Myocardial infarction within 6 months prior to Cycle 1 Day 1 (C1D1), and/or prior diagnoses of congestive heart failure (New York Heart Association Class III or IV), unstable angina, unstable cardiac arrhythmia requiring medication; and/or the subject is at risk for polymorphic ventricular tachycardia (eg, hypokalemia, family history, or long QT syndrome)
- 8. Uncontrolled hypertension, defined as systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 100 mmHg confirmed upon repeated measures
- 9. Left ventricular ejection fraction (LVEF) $<$ 40% as determined by echocardiogram (ECHO)/multigated acquisition scan (MUGA) performed at screening or within 90 days prior to C1D1
- 10. QT/QTc interval $>$ 450 msec, as determined by screening ECG performed no earlier than 1 week before C1D1
- 11. Prior anti-tumor therapy (chemotherapy, radiotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, or hormonal therapy) within 4 weeks ($<$ 28 days) prior to C1D1
- 12. Major surgery within 4 weeks ($<$ 28 days) prior to C1D1
- 13. Active joint inflammation or history of inflammatory arthritis or other immune disorder involving joints (osteoarthritis is not exclusionary)
- 14. Active infection involving IV antibiotics within 2 weeks prior to C1D1
- 15. Known history of or active hepatitis B virus (HBV) and/or hepatitis C virus (HCV), or active tuberculosis
- 16. Known history of human immunodeficiency virus (HIV) type 1/2 or other immunodeficiency disease
- 17. Subject has received a live vaccine within 4 weeks ($<$ 28 days) prior to C1D1
- 18. Known hypersensitivity to any component of recombinant protein production by Chinese Hamster Ovary (CHO) cells
- 19. Exposure to an investigational product or investigational device in another clinical study within 4 weeks ($<$ 28 days) prior to C1D1, or is scheduled to participate in another clinical study involving an investigational product or device during the course of this study
- 20. Subject is breastfeeding or intends to begin breastfeeding during the course of the study

21. Any disorder or disease, or clinically significant abnormality on laboratory or other clinical test(s) (eg, blood tests, ECG), that in medical judgment of the investigator may impede the subject's participation in the study, pose increased risk to the subject, and/or confound the results of the study
22. Subject is a family member or employee of the investigator

STATISTICAL ANALYSIS

Sample Size Calculations

Part 1: The final sample size in the Safety Run-in phase is dependent on the pre-stated rules of the dose escalation study design (see Section 8.1). In Part 1, the sample size for each dosing regimen (ie, imalumab + 5-FU/LV and imalumab + panitumumab) is expected to be between 6 and 12 subjects (ie, 3 to 6 subjects at each imalumab dose level). Non-evaluable subjects will be replaced to meet study objectives.

Part 2: The primary exploratory efficacy endpoint will be PFS. Assuming that the median PFS is 2.4 months in the control arm and 4.25 months in the experimental arm (hazard ratio 0.565), and using a one-sided α of 0.15 and β of 0.20 with a drop-out rate of 20% at 6 months, 48 PFS events are needed. With an enrollment ratio of 2:1, and taking into account the time for accrual of 1 year and an additional follow-up period of 6 months after the last subject is enrolled, the sample size needed is a total of 44 subjects in the imalumab-containing treatment arms and 22 subjects in the control arm (SoC), for a total of 66 subjects.

Planned Statistical Analysis

In general, descriptive summaries will be presented for the safety and immunogenicity variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables, Kaplan-Meier (KM) plots, median time-to-event, and other percentiles will be presented. For the primary efficacy endpoint PFS, the one-sided p-value from log rank test will be presented. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term. In addition, summaries of AEs by severity and relationship to study drug will be presented.

Where appropriate, some measures will be summarized by both point estimates and estimation of 95% confidence intervals (CIs).

An interim analysis will be implemented for planning purposes when 33 PFS events have been observed. The interim analysis will primarily include a summary of safety (as measured by incidence of TEAEs) and PFS by treatment arm. The DSMB will be included in review of the interim analysis data.

More detailed information about estimation of treatment effects, summarization of data, graphical representations, and analysis conventions will be provided in the imalumab Statistical Analysis Plan.

4. TABLE OF CONTENTS

1. STUDY PERSONNEL	2
1.1 Authorized Representative (Signatory) / Responsible Party	2
1.2 Study Organization.....	2
2. SERIOUS ADVERSE EVENT REPORTING.....	3
3. SYNOPSIS.....	4
4. TABLE OF CONTENTS	13
5. LIST OF ABBREVIATIONS	19
6. BACKGROUND INFORMATION	23
6.1 Description of Investigational Product	23
6.1.1 Macrophage Migration Inhibitory Factor (MIF)	23
6.1.2 The Role of MIF in Cancer	23
6.1.3 Imalumab, Anti-Macrophage Migration Inhibitory Factor Antibody.....	24
6.1.4 Genetic Biomarkers Analysis.....	25
6.1.5 Rationale for Dose, Treatment Period, and Dosing Frequency.....	26
6.1.5.1 Dose Rationale.....	26
6.1.5.2 Treatment Duration Rationale	26
6.1.5.3 Rationale for Dosing Frequency	26
6.1.5.4 Rationale for Selection of Combination Therapies	27
6.2 Clinical Condition/Indication	27
6.3 Population to be Studied	28
6.4 Findings from Nonclinical and Clinical Studies.....	28
6.4.1 Non-Clinical Summary.....	28
6.4.2 Clinical Summary	30
6.4.2.1 Clinical Protocol 391101.....	30
6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects.....	33
6.6 Compliance Statement.....	33
7. STUDY PURPOSE AND OBJECTIVES	34
7.1 Study Purpose	34
7.2 Primary Objectives	34
7.3 Secondary Objectives	34
7.3.1 Efficacy	34
7.3.2 Safety.....	35

7.3.3 Pharmacokinetics.....	35
7.3.4 Quality of Life	35
7.4 Exploratory Objectives.....	35
7.4.1 Pharmacodynamics.....	35
7.4.2 Genetic Biomarkers	35
7.4.3 Quality of Life	35
8. STUDY DESIGN.....	36
8.1 Brief Summary.....	36
8.2 Overall Study Design	36
8.2.1 Part I: Safety Run-In.....	36
8.2.1.1 Stopping Criteria for Dose Escalation	37
8.2.2 Part 2: Exploratory Phase 2a.....	38
8.2.3 Definition of Dose-Limiting Toxicity	38
8.3 Duration of Study Period(s) and Subject Participation	39
8.4 Outcome Measures	39
8.4.1 Primary Outcome Measure	39
8.4.2 Secondary Outcome Measures	40
8.4.2.1 Immunogenicity Outcome Measures	40
8.4.2.2 Safety Outcome Measures.....	40
8.4.2.3 Efficacy Outcome Measures	40
8.4.2.4 Pharmacokinetic Outcome Measures	40
8.4.2.5 Quality of Life Outcome Measures	40
8.4.3 Exploratory Outcomes Measure	40
8.5 Randomization and Blinding	41
8.6 Study Stopping Rules.....	41
8.7 Investigational Product and Standard Drugs	41
8.7.1 Packaging, Labeling, and Storage	41
8.7.1.1 Imalumab	41
8.7.1.2 Leucovorin.....	42
8.7.1.3 5-Fluorouracil	42
8.7.1.4 Panitumumab.....	42
8.7.1.5 Standard of Care (Investigator Choice)	42
8.7.2 Preparation and Storage of Pooled Product	43
8.7.2.1 Imalumab	43
8.7.2.2 5-Fluorouracil, Leucovorin, and Panitumumab	44
8.7.2.3 Standard of Care Drugs	44
8.7.3 Administration	44
8.7.3.1 Imalumab	44
8.7.3.2 5-Fluorouracil, Leucovorin, and Panitumumab	44
8.7.3.3 Standard of Care Drugs	45
8.7.4 Description of Treatment	45
8.7.4.1 Part 1: Safety Run-In	45
8.7.4.2 Part 2: Exploratory Phase 2a.....	45

8.7.5 Investigational Product Accountability	46
8.8 Source Data	46
9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION	47
9.1 Inclusion Criteria.....	47
9.2 Exclusion Criteria.....	48
9.3 Withdrawal and Discontinuation	50
10. STUDY PROCEDURES	51
10.1 Informed Consent and Enrollment	51
10.2 Subject Identification Code.....	51
10.3 Screening and Study Visits.....	51
10.3.1 Screening Assessments	51
10.3.2 Baseline Assessments (Cycle 1 Day 1, Predose)	53
10.3.3 Treatment Cycles	53
10.3.3.1 Study Drug Administration	54
10.3.3.2 Day 1 of Each Cycle.....	56
10.3.3.3 Day 8 of Each Cycle.....	57
10.3.3.4 Day 15 of Each Cycle.....	58
10.3.3.5 Day 22 of Each Cycle.....	60
10.3.3.6 Day 28 (Cycle 1 and then Every Other Cycle)	60
10.3.3.7 Day 28 (Cycle 2 and then Every Other Cycle)	61
10.3.3.8 End of Study/Early Termination Visit.....	61
10.3.3.9 Safety Follow-Up Visit.....	62
10.3.3.10 Survival Follow-Up (Post Therapy)	63
10.4 Medications and Non-Drug Therapies.....	63
10.5 Subject Completion/Discontinuation	63
10.6 Procedures for Monitoring Subject Compliance	64
11. ASSESSMENT OF EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND GENETIC TESTING.....	64
11.1 Plasma Imalumab, oxMIF, and Total MIF	64
11.2 Antitumor Effect – Solid Tumors.....	65
11.3 Genetic Testing.....	65
11.4 Tumor-Associated Biomarkers.....	66
12. ASSESSMENT OF SAFETY	66
12.1 Adverse Events	66
12.1.1 Definitions.....	66
12.1.1.1 Serious Adverse Event.....	67
12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR).....	68
12.1.1.3 Non-Serious Adverse Event	68

12.1.1.4 Unexpected Adverse Events.....	68
12.1.1.5 Preexisting Diseases	69
12.1.2 Assessment of Adverse Events.....	69
12.1.2.1 Severity	70
12.1.2.2 Causality	71
12.1.2.3 Safety Reporting	72
12.2 Urgent Safety Measures	73
12.3 Untoward Medical Occurrences.....	74
12.4 Non-Medical Complaints	74
12.5 Medical, Medication, and Non-Drug Therapy History	75
12.6 Physical Examinations.....	75
12.7 Clinical Laboratory Parameters.....	75
12.7.1 Hematology and Clinical Chemistry	75
12.7.2 Urinalysis	76
12.7.2.1 Assessment of Laboratory Values	76
12.8 Vital Signs.....	77
12.9 Electrocardiograms	77
 13. STATISTICS	78
13.1 Sample Size and Power Calculations	78
13.2 Datasets and Analysis Cohorts	78
13.3 Handling of Missing, Unused, and Spurious Data.....	78
13.4 Methods of Analysis.....	78
13.4.1 General Considerations.....	78
13.4.2 Demographics and Other Subject Characteristics	79
13.4.3 Primary Outcome Measure.....	80
13.4.3.1 Primary Safety Outcome Measure.....	80
13.4.3.2 Primary Efficacy Outcome Measure	80
13.4.4 Secondary Outcome Measures	80
13.4.4.1 Immunogenicity Outcome Measures	80
13.4.4.2 Safety Outcome Measures.....	81
13.4.4.3 Secondary Efficacy Outcome Measures	82
13.4.4.4 Secondary Pharmacokinetic Outcome Measure.....	82
13.4.4.5 Secondary Quality of Life Outcome Measures	82
13.4.5 Exploratory Outcome Measures	82
13.5 Planned Interim Analysis of the Study	83
 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	83
 15. QUALITY CONTROL AND QUALITY ASSURANCE.....	83
15.1 Investigator's Responsibility.....	83
15.1.1 Final Clinical Study Report	84
15.2 Training	84

15.3 Monitoring	84
15.4 Safety Monitoring	84
15.4.1 Data Safety Monitoring (Part 1).....	84
15.4.2 Data Safety Monitoring Board (Part 2)	85
15.5 Auditing	85
15.6 Non-Compliance with the Protocol	85
15.7 Laboratory and Reader Standardization	85
16. ETHICS	86
16.1 Subject Privacy	86
16.2 Ethics Committee and Regulatory Authorities	86
16.3 Informed Consent	86
17. DATA HANDLING AND RECORD KEEPING.....	87
17.1 Confidentiality Policy	87
17.2 Study Documentation and Case Report Forms	87
17.3 Document and Data Retention.....	88
18. FINANCING AND INSURANCE.....	88
19. PUBLICATION POLICY.....	88
20. SUPPLEMENTS	89
20.1 Study 391401 Schematic	89
20.2 Schedule of Study Procedures and Assessments	90
21. REFERENCES.....	106
22. SUMMARY OF CHANGES	110

Tables

Table 1 Study 391401: Management of Imalumab Injection-Related Reactions	55
Table 2 Mapping Conventions for AE Severity (For AEs Not Described Within NCI CTCAE)	70
Table 3 Schedule of Study Procedures and Assessments: Parts 1 and 2	90
Table 4 Schedule of Study Procedures and Assessments: SoC Following Randomization (4-Week Cycles or if Subject is on Best Supportive Care).....	95
Table 5 Schedule of Study Procedures and Assessments: SoC Following Randomization (3-Week Cycles)	99

Table 6 Schedule of Pharmacokinetic and Pharmacodynamic Sample Collections (Parts 1 and 2) for Subjects Receiving Imalumab Treatment	103
Table 7 Blood Volumes (Parts 1 and 2) for Lab Tests and PK/PD for Subjects Receiving Imalumab Treatment.....	104
Table 8 Blood and Urine Volumes (Parts 1 and 2) for Optional Genetic Biomarkers cfDNA Analysis for Subjects Receiving Imalumab Treatment.....	105

Figures

Figure 1 Protocol 391401 Dose Escalation Scheme	37
Figure 2 Study 391401 Schematic	89

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
anti-MIF	anti-macrophage migration inhibitory factor
anti-oxMIF	anti-oxidized macrophage migration inhibitory factor
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration vs time curve
AUC ₀₋₃₃₆	area under the concentration vs time-curve from time zero to 336 hours
AUC _{0-inf}	area under the concentration vs time-curve from time zero to infinity
AUC _{0-tau}	area under the concentration vs time-curve from time zero to time tau over a dosing interval at steady state
BRAF	B-Raf proto-oncogene, serine/threonine kinase
C1D1	Cycle 1 Day 1
C2D15	Cycle 2 Day 15
CBR	clinical benefit rate
cfDNA	cell-free DNA
CHO	Chinese Hamster Ovary
CI	confidence interval
CL	clearance
C _{max}	maximum observed concentration
C _{min}	minimum observed concentration
CRC	colorectal cancer
CRF	case report form
CRP	C-reactive protein
CT	computerized tomography
CTA	Clinical Trial Agreement
CXCR	C-X-C chemokine receptor
DLT	dose-limiting toxicity
DRC	Data Review Committee

Abbreviation	Definition
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-CR29	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for colorectal cancer 29
EQ-5D	European Quality of Life – 5 Dimensions
ERK1	extracellular signal-regulated kinase 1
ERK2	extracellular signal-regulated kinase 2
FAS	Full Analysis Set
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IL	interleukin
INR	International Normalized Ratio
IP	investigational product
IRT	Interactive Response Technology
IV	intravenous(ly)
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
KRAS mut	mutated Kirsten rat sarcoma viral oncogene homolog
KRAS wt	wild type Kirsten rat sarcoma viral oncogene homolog
LV	leucovorin
LVEF	left ventricular ejection fraction
mCRC	metastatic colorectal cancer

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency (UK)
MIF	macrophage migration inhibitory factor
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
mut	mutated
NADA	neutralizing anti-drug antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NMC	non-medical complaint
NOAEL	no observed adverse effect level
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog
ORR	overall response rate
OS	overall survival
oxMIF	oxidized macrophage migration inhibitory factor
PD	pharmacodynamic
PEI	Paul-Ehrlich-Institute
PFS	progression-free survival
PK	pharmacokinetic
PS	performance status
QoL	quality of life
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
Q2W	every 2 weeks
QW	every week
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RSI	Reference safety information
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
US CFR	US Code of Federal Regulations
V_{dss}	volume of distribution at steady state
wt	wild type

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

6.1.1 Macrophage Migration Inhibitory Factor (MIF)

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that acts as a critical upstream regulator of the inflammatory cascade, influences adaptive immune responses, and is a pivotal regulator of innate immunity.^{1; 2} MIF is secreted by the anterior pituitary gland and from pre-formed stores in immune cells in response to injury, infection, and cellular stress.^{2; 3} MIF promotes the release of other cytokines (such as tumor necrosis factor- α , INF- γ , interleukin [IL]-1 β , IL-6, IL-8) and plays a central role in autocrine/paracrine activation of macrophages.^{2; 4} MIF is implicated in the pathogenesis of inflammatory and autoimmune diseases, which have been associated with certain allelic variants of the human MIF gene⁵ as well as with elevated levels of MIF in serum.^{6; 7; 8}

MIF displays also a number of functions that promote tumor progression: (i) MIF acts directly on tumor cells by activating signaling pathways that promote cell proliferation and cell survival. (ii) MIF facilitates invasion of the extracellular matrix and induces angiogenesis and tumor vascularization. (iii) As a pro-inflammatory cytokine, MIF is one of the mediators of tumor micro-inflammation. Inflammatory-mediated events such as the production of reactive, cytotoxic molecules and growth factors as well as the activation of signal-transduction pathways that promote cell survival and proliferation, are proposed to be important factors in cancer progression.⁹ MIF has been shown to be up-regulated in a large variety of human neoplasms (eg, pancreatic, breast, prostate, colon, brain, skin, and lung-derived tumors),^{10; 11; 12} where it is thought to contribute to tumor growth, angiogenesis, invasiveness, and metastases spread. Indeed, anti-MIF antibodies have been shown to effectively inhibit tumorigenesis and angiogenesis in a variety of animal models.^{13; 14; 15}

6.1.2 The Role of MIF in Cancer

MIF is involved in the regulation of tumor-suppressor genes, angiogenesis, and cell senescence. Tumor progression is supported by several MIF activation responses including sustained extracellular signal-regulated kinase (extracellular signal-regulated kinase 1 [ERK1] and extracellular signal-regulated kinase 2 [ERK2]) activation, inhibition of p53-mediated growth arrest and apoptosis, increased hypoxia-inducible factor-1 α , and delayed tumor cell senescence. Increased angiogenic factor production (eg, vascular endothelial growth factor) and increased matrix metalloproteinase secretion facilitate tumor invasion. Additionally MIF dependent activation of CD44 enhances the

metastatic process.⁹ MIF binds to CD74 surface protein that leads to CD44-dependent activation of Src-family receptor tyrosine kinases. MIF can also bind and signal through G-protein coupled chemokine receptors (C-X-C chemokine receptor [CXCR] 2 and CXCR4). However, the precise expression and functional profile of the MIF-receptor complexes have not yet been resolved.¹⁶

Several studies also report that MIF expression closely correlates with tumor aggressiveness and metastatic potential, suggesting that MIF may play an important role in disease severity and cell survival.¹⁷ Recent data suggest that extracellular MIF may contribute to a more aggressive tumor phenotype as compared to intracellular MIF,¹⁸ which is not accessible to neutralization by antibodies. Neutralizing anti-MIF antibodies have been shown to effectively inhibit tumorigenesis in animal models of B cell lymphoma, prostate cancer and colon cancer.^{13; 14; 15}

MIF has been shown to be up-regulated in a large variety of human neoplasms, including colorectal cancer (CRC).¹⁹ The concentration of serum MIF was positively correlated with an increased risk of hepatic metastasis in subjects with CRC. MIF was also dramatically up-regulated in human colorectal tissue, with 20–40 times as many MIF-positive cells found in the mucosa of subjects with CRC than in normal tissues.¹⁹ Given the association between MIF and CRC, various animal studies have examined MIF as a potential therapeutic target in this disease. Mice bearing CT26 colon carcinoma cell transplants were treated with neutralizing anti-MIF antibodies and a significant reduction in tumor burden and tumor-associated angiogenesis was observed relative to vehicle-treated animals.^{15; 19} Furthermore, studies demonstrated that tumor growth rate was significantly lower in MIF knockout (MIF^{-/-}) mice than in wild-type (MIF^{+/+}) mice.²⁰ In summary, there is mounting evidence to suggest that MIF may play a key role in CRC.

6.1.3 Imalumab, Anti-Macrophage Migration Inhibitory Factor Antibody

Imalumab is a recombinant, fully human antibody specific for the active form of the MIF molecule. Imalumab is expressed in a Chinese Hamster Ovary (CHO) cell line using plasma protein-free production process. The antibody consists of two heavy chains of the gamma-1 isotype, and 2 kappa light chains and shows structural features typical for human IgG-1/kappa. Each heavy chain carries 1 N-glycan. Imalumab, formulated as a sterile, nonpyrogenic, liquid preparation in 250 mM glycine buffer pH 5.0, is stable within a protein concentration range of 50 – 100 mg anti-oxidated macrophage migration inhibitory factor (anti-oxMIF)/mL. During formulation development, imalumab stability in a liquid formulation was demonstrated. Results showed constant functional activity

(demonstrated by anti-oxMIF enzyme-linked immunosorbent assay) and no increase of aggregates (confirmed by dynamic light scattering) when stored at 4°C. There was only a modest increase in dimers by 0.03% per month with a corresponding decrease for monomers (size exclusion high performance liquid chromatography data confirmed by asymmetric flow field fractionation) (Imalumab Formulation Development Report RD_PPD_120902).²¹

6.1.4 Genetic Biomarkers Analysis

Studies of metastatic colorectal cancer (mCRC) demonstrated that KRAS/NRAS-status can change during therapy and that KRAS/NRAS-mutation can be found by cell-free DNA (cfDNA) interrogation in patients originally KRAS/NRAS-wild type (wt).²² Molecular alterations (in most instances point mutations) of KRAS are causally associated with the onset of acquired resistance to anti-epidermal growth factor receptor (EGFR) treatment in colorectal cancers. Analysis of metastases from patients who developed resistance to cetuximab or panitumumab showed the emergence of KRAS amplification in one sample and acquisition of secondary KRAS mutations in 60% (6/10) of cases. KRAS mutant alleles were detectable in the blood of cetuximab-treated patients as early as 10 months prior to radiographic documentation of disease progression.²³ It has been demonstrated that the primary tumor – identified by conventional tumor-tissue KRAS tests – is not consistently representative of the related metastasis, especially when considering treatment of mCRC. This suggests the need for re-biopsy of metastases or, preferably, for an efficient blood test to adjust the predictive value of KRAS status in response to anti-EGFR therapy in patients with mCRC at the time of decision making. In addition, cfDNA analysis enables the noninvasive detection of the emergence of KRAS mutations as drivers of acquired resistance to panitumumab in mCRC.

Therefore, subjects with mCRC in this study will be monitored using cfDNA methodologies for a change in KRAS/NRAS status from KRAS/NRAS-wt to KRAS/NRAS-mutated (mut).

Numerous studies have shown that patients treated with an anti-EGFR tyrosine kinase inhibitor (erlotinib or gefitinib) can acquire resistance to these therapies, which is associated with the development of T790M mutations. Several studies have also shown that cfDNA can be used to identify B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations in patients receiving BRAF inhibitors.^{24; 25; 26; 27}

Thus, in addition to the KRAS gene, a larger cancer gene panel will be tested by either targeted next generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) using tumor-derived cfDNA in order to identify imalumab-specific patterns of

genetic tumor adaption/mechanisms resistance. Results from the cfDNA analyses might also be used to verify tumor burden.²⁸

6.1.5 Rationale for Dose, Treatment Period, and Dosing Frequency

6.1.5.1 Dose Rationale

As of 2015 JUL 01, preliminary Phase 1 data indicate that imalumab was generally well tolerated up to a dose of 37.5 mg/kg every 2 weeks (Q2W) and 25 mg/kg every week (QW). The observed dose-limiting toxicity (DLT) occurred in a subject treated with 50 mg/kg Q2W. Pharmacokinetic (PK) assessment generally showed a linear increase over the imalumab dose range.

The 7.5 mg/kg and 10 mg/kg starting doses in Part 1 of this study were selected as a result of the preliminary Phase 1 data and represent at least an approximate of 2.5-fold safety factor (based on area under the concentration vs time-curve from time zero to time tau over a dosing interval at steady state [$AUC_{0-\tauau}$]) in comparison to the dose at which the observed DLT occurred in a subject in Study 391101 treated with 50 mg/kg Q2W.

During Arm 2 of the Phase 1 study in mCRC subjects, biopsies from liver metastases were collected from subjects treated with 10 or 25 mg/kg QW to study drug penetration and target saturation. Preliminary results show an accumulation over time of treatment of imalumab within the tumor cells and the surrounding stroma, with a mean of approximately 100% target occupancy after the first cycle of treatment (n=3 subjects at 10 mg/kg QW). At 25 mg/kg QW (n=1), a comparable target occupancy was detected in the tumor after the first treatment cycle, but imalumab was also detected in adjacent normal liver tissue. Thus, these data support the rationale for 10 mg/kg QW dose as a treatment regimen for the Phase 2a study.

6.1.5.2 Treatment Duration Rationale

Subjects will be treated until disease progression, unacceptable toxicity, death or subject withdrawal of consent, whichever occurs first (see Section 9.3).

6.1.5.3 Rationale for Dosing Frequency

The QW dosing frequency was selected using preliminary Phase 1 PK data (Study 391101) showing that optimal tissue saturation could be obtained with the QW dosing relative to the Q2W dosing. The half-life of imalumab ranged from 3.3 to 10.8 days (ie, around a range of approximately 1 week), indicating that QW dosing is preferable to Q2W dosing for maintaining more stable concentrations of imalumab. For

the 10 mg/kg dose, C_{\max}/C_{\min} ratios (peak/trough fluctuation) on Day 15 of Cycle 2 were approximately 4-fold for QW dosing compared with 7.5-fold for Q2W dosing.

6.1.5.4 Rationale for Selection of Combination Therapies

5-Fluorouracil and Leucovorin

The options for third- or fourth-line treatment are few, and 5-fluorouracil (5-FU)/leucovorin (LV) is part of standard of care (SoC). This regimen can be given regardless of Kirsten rat sarcoma viral oncogene homolog (KRAS) status and is well tolerated in this late-line setting when quality of life becomes an important parameter.

Panitumumab

Panitumumab is an approved option for third or fourth line monotherapy for subjects with KRAS wt tumors. Recently, using the novel technique of massively parallel multigene sequencing (also known as NGS), it has been shown that patients who benefit from panitumumab are those with all-RAS wt tumors, ie, those with no mutation in KRAS and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) exons 2, 3, 4 at codons 12, 13, 61, 117, 141.^{29; 30; 31} The role of BRAF mutation as predictive of responsiveness to anti-EGFR monoclonal antibodies remains to be further validated. On the other hand, panitumumab is better tolerated than cetuximab because it is a fully humanized monoclonal antibody and it is better tolerated than another approved targeted agent, regorafenib, which yields severe toxicity in the majority of subjects. In this study, subjects will be tested for KRAS and NRAS mutation status, and only those with all-RAS wt tumor will be eligible for treatment with panitumumab.

Panitumumab has been approved in several countries including the United States (US) and Germany as standard therapy. The sponsor feels it is justified to administer panitumumab to subjects in this study with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2. Panitumumab has been shown to be well tolerated in frail elderly patients (ECOG ≤ 3) with KRAS wt mCRC and poor prognostic factors in a Phase 2 study of the Spanish Cooperative Group for the Treatment of Digestive Tumours.³² In addition, panitumumab and cetuximab were compared in a randomized Phase 3 study in patients with chemotherapy-refractory KRAS wt mCRC (ECOG ≤ 2).³³ The incidence of adverse events (AEs) of any grade and grade 3-4 AEs was similar across treatment groups.

6.2 Clinical Condition/Indication

In this study, imalumab is intended for treatment of mCRC as third- or fourth-line therapy.

6.3 Population to be Studied

Male and female subjects aged 18 years or older with a confirmed diagnosis of mCRC are eligible if they have progressed after receiving at least 2, but no more than 3, prior treatment lines including SoC, and have an ECOG PS of 0-2. Adjuvant therapy in the metastatic setting (administered following a surgical procedure) and investigational products are included in the definition of a prior line of treatment for the purposes of this study.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Non-Clinical Summary

A summary of non-clinical toxicology findings is provided below. Refer to the imalumab Investigator's Brochure (IB) for additional details.

In a single-dose cardiovascular safety pharmacology study (Study 8240906), telemetered cynomolgus monkeys were administered a single dose of imalumab at 25, 50, or 200 mg/kg (Day 1). No adverse effects on cardiovascular or respiratory parameters were detected at doses of 25 and 50 mg/kg. Increased blood pressure (mean change of ~10%) and heart rate (mean change of ~30%) with corresponding shortened corrected QT interval (QTc) (mean change of ~10%) was measured by telemetry at the highest dose (200 mg/kg).

In the same study, full necropsy and histopathological evaluation of the large and small joints were performed at study termination (Day 6). Treatment with imalumab was associated with adverse clinical signs from Day 1 to 4 in one animal of the high dose group (200 mg/kg) including abnormal movement, hypoactivity, prostration, and tremor. Inflammation of the joints of the knee, elbow, tarsus, and phalanges (hand and foot) of animals treated at 50 or 200 mg/kg were considered to be test-item related. This inflammation consisted of acute to subacute inflammation of the synovia, ligaments, and muscle, villous hyperplasia of the synovia and hemorrhage in the joints of knee, elbow and tarsus. In the phalanges of the hands and feet, acute to subacute inflammation of the tendons and tendon sheath, as well as subcutaneous inflammation with scab and ulcer, were obvious. Test-item related histopathological findings in the elbow joint of 2/4 animals of the low dose group (25 mg/kg) consisted of bilateral moderate hemorrhage (in 1 animal) and slight inflammation of the synovial and ligaments. A dose-related increase in incidence and severity was observed with inflammation. Based on these findings, a no observed adverse effect level (NOAEL) could not be determined under the conditions of this study.

In cynomolgus monkeys, no adverse effects were detected at 25 mg/kg in the 1-month repeated toxicity study. However, dose-dependent, test-item-related events were evident at doses \geq 100 mg/kg as transient clinical signs (transient waddling gait, squatted posture and reduced activity) with onset 2 to 3 days post first dose. These observations resolved spontaneously, within 7 days of test-item administration. No clinical signs were observed following subsequent (second to fifth) doses. At the end of the 1-month dosing regimen, animals were sacrificed for histopathology either immediately, or following a 4-week recovery period (high dose and control animals only). Of the animals sacrificed immediately, monkeys of the 50, 100 and 200 mg/kg imalumab dose groups demonstrated histopathological changes in knee joints, which were likely responsible for the clinical signs observed following the first dose. These changes were characterized as acute or subacute inflammation of the synovial membrane and the cruciate and patellar ligament and villous hyperplasia of the synovial membrane. Partial recovery of these histopathological changes was evident in the monkeys of the high dose group sacrificed after a 4-week treatment-free period (lower severity and incidence). In addition, ligament lesions were not detected following the recovery period. No deaths occurred during either the dosing or the recovery phases.

Cynomolgus monkeys were injected intravenously over a 6-month period with weekly doses of imalumab at dose levels of 10, 25, or 50 mg/kg, in a repeated dose chronic toxicity study with full fertility assessment (Study 8275958). Recovery groups (for all groups) for a period of 8 weeks were included. Administration with imalumab over 26 weeks had no toxicologically relevant effects on body weight, clinical observations, body temperature, serum chemistry, hematology, coagulation, urine, menstrual cycle, testicular size, semen evaluation, spermatogenesis, or hormone parameters. Additionally, no ophthalmic findings were recorded. Cytokine analyses indicated there was a slight to moderate IL-6 response after the first, second, and last dose administered at the end of the dosing phase in the high-dose and intermediate-dose groups (up to 56.3 pg/ml). Group differences were statistically significant for male animals of the high-dose group and the intermediate-dose group (only after administration of the last dose). Elevations of serum IL-6 levels were transient in all individuals and returned to baseline values (or were below detectable limit) at 168 hours after imalumab administration. The timing of these transient changes in IL-6 serum levels, which reached statistical significance at 4 hours and 24 hours post dose, in combination with the histopathological findings discussed below, suggest that these effects are likely to be related to imalumab administration. Highest C-reactive protein (CRP) values were detected for 2 high-dose group animals, showing histopathologically adverse effects for multiple joints; however, no clear dose dependency or correlation between CRP and histopathological results were apparent. At

the end of the dosing phase, microscopic findings were confined to the synovial membrane and adjacent ligaments and/or tendons in single or multiple joints, including the knee, elbow, tarsus, and phalanges of 3 intermediate-dose group and 6 high-dose group animals. These lesions were attributed to administration of imalumab. Findings consisted of subacute inflammation and villous hyperplasia of the synovial membrane (in the knee, elbow, and tarsus joints), subacute inflammation of the ligament (in the knee) and subacute inflammation of the ligament and of the tendon sheath (in the tarsus). In the phalanges of the hand and foot, subacute inflammation of the tendons and tendon sheath and/or subacute inflammation and villous hyperplasia of the synovial membrane and/or sub-acute inflammation of the ligament were also noted. The severity and incidence of the findings were more prominent in male animals. After the recovery phase, histopathological findings in 1 intermediate-dose group and 2 high-dose group animals were present in the larger joints (knee, elbow, and tarsus), as well as in the middle finger and little toe. These consisted of villous hyperplasia and inflammation of the synovial membranes and inflammation of the ligament and tendon, which was also seen in terminal killed animals. In addition to the above findings, ossification of the tendon sheath (tarsus) and ligament (elbow) was restricted to 1 high-dose group female of the recovery phase.

In rats, no adverse effects were detected following 5 consecutive weekly doses of up to 250 mg/kg imalumab over a period of 1 month.

In summary, while no NOAEL was observed during the single-dose studies, repeat-dose toxicity studies in rats and cynomolgus monkeys demonstrated a NOAEL of 250 mg/kg in rats and 25 mg/kg (1 month) and 10 mg/kg (6 months) in cynomolgus monkeys.

6.4.2 Clinical Summary

6.4.2.1 Clinical Protocol 391101

As of the date of this protocol, imalumab is being evaluated in subjects with malignant solid tumors including metastatic adenocarcinoma of the colon or rectum, metastatic non-small cell lung cancer and metastatic ovarian cancer. Study 391101 is a Phase 1, multicenter open-label dose-escalation study to assess the safety, tolerability, PK, pharmacodynamics (PD), tumor penetration, and target binding of imalumab as a single agent in approximately 36 to 60 evaluable subjects. The 2-treatment-arm study design includes dose escalation with imalumab administered intravenously (IV) over a 28-day treatment cycle, as a single agent Q2W (Arm 1) and QW (Arm 2). The imalumab maximum administered dose (MAD) of single agent imalumab was 50 mg/kg in the Q2W

schedule. The expansion phase is ongoing with the QW schedule (mCRC, non-small cell lung cancer, and ovarian cancer).

As of 2015 JUL 01, a total of 48 subjects (28 subjects in the dose escalation phase and 20 subjects in the expansion cohort) have received doses ranging from 1 mg/kg to 50 mg/kg IV Q2W, and a total of 18 subjects in the dose escalation phase have received doses ranging from 10 to 25 mg/kg IV QW.

6.4.2.1.1 Safety Summary

Imalumab appears to be safe and well tolerated up to a dose of 37.5 mg/kg Q2W and 25 mg/kg QW. As of the 2015 JUL 01 cut-off date, one suspected unexpected serious adverse reaction (SUSAR) was reported. Following administration of imalumab, a PPD [REDACTED] male with mCRC experienced an unspecified infusion reaction. Seventy-two hours later, the subject presented symptoms of shortness of breath with pleuritic chest pain. The subject's diagnostic and clinical evaluation was consistent with hypersensitivity pneumonitis without evidence of infection or hemorrhage. This serious adverse reaction of hypersensitivity pneumonitis (Medical Dictionary for Regulatory Activities [MedDRA] preferred term: alveolitis allergic), which also met the protocol-defined criteria for dose-limiting toxicity, occurred after administration of the maximum administered dose of 50 mg/kg Q2W of imalumab. Consequently, enrollment in the 50 mg/kg Q2W cohort was discontinued, and 3 additional subjects were enrolled at the dose level immediately below 50 mg/kg Q2W (ie, 25 mg/kg Q2W) to collect additional safety data. Data from these 3 additional subjects were reviewed by the Data Review Committee (DRC) and investigators. Because no safety issues or concerns were noted, it was decided to dose escalate to 37.5 mg/kg Q2W (Cohort 5a) rather than to 50 mg/kg Q2W. All 3 subjects in Cohort 5a completed at least 1 treatment cycle and no DLTs were reported at doses up to 37.5 mg/kg Q2W.

Subsequently, Arm 2 was initiated. In Cohort 7, a total of 6 subjects with mCRC received imalumab 10 mg/kg QW. The additional 3 subjects at the 10 mg/kg QW dose level in Cohort 7 were enrolled to further collect PD markers. In Cohort 8, 3 subjects with mCRC received imalumab 25 mg/kg QW. In Cohort 10, a total of 20 subjects received imalumab 10 mg/kg QW, including 8 with mCRC, 8 with ovarian cancer, and 4 with NSCLC. As of 2015 JUL 01, no DLTs were reported for any subjects treated with imalumab QW (Arm 2) (preliminary data).

One additional SUSAR of Grade 3 nausea, vomiting, and constipation was reported in the 391101 Phase 1 study after the data cut-off date (2015 JUL 01) on 2015 SEP 16, which occurred after 1 cycle of imalumab 10 mg/kg QW. The Investigator assessed that this

serious adverse reaction was possibly related to imalumab, with constipation more likely to be related to the underlying disease. The most frequent related AEs experienced by the subjects were fatigue (8.4%), constipation (6.3%), dysgeusia (4.2%), and rash (4.2%) (as of 2015 JUL 01 data cut-off). The majority of related AEs were determined by the investigator to be mild or moderate, and many of these events were confounded by the underlying ailment; however, the events were evaluated taking a conservative approach, and the events were considered related. Overall, 15 (31.3%) subjects reported a total of 22 serious adverse events (SAEs) (preliminary data as of 2015 JUL 01). Please refer to the IB for additional information.

6.4.2.1.2 Pharmacokinetic Summary

Imalumab concentration-time profiles in Arms 1 and 2 showed a bi-exponential decline following single and multiple dose administration. In Arm 1 (Q2W), trough (predose) concentrations indicated that some subjects achieved steady state by treatment Cycle 2 Day 15 (C2D15), while others continued to show an increase in concentration up until the end of Cycle 3 (ie, 84 days after the start of treatment).

Across both Arms 1 (Q2W) and 2 (QW), geometric mean half-life ($t_{1/2}$) ranged from 3.3 to 8.1 days on Cycle 1 Day 1 (C1D1) and 4.1 to 10.8 days on C2D15; estimates of $t_{1/2}$ appeared to be generally independent of dose over the dose range evaluated. Estimates of $t_{1/2}$ may be underestimated for longer estimates of $t_{1/2}$ and in Arm 2.

Imalumab exposure in Arm 1 (maximum observed concentration [C_{max}]), area under the concentration vs time-curve from time zero to infinity [AUC_{0-inf}], and area under the concentration vs time-curve from time zero to 336 hours [AUC_{0-336}] on C1D1, and C_{max} and AUC_{0-336} on C2D15) showed a generally linear increase over the dose range. A similar linear increase was observed for C_{max} , AUC_{0-inf} , and AUC_{0-336} on C1D1 in Arm 2. There was a larger degree of variability in exposure at the higher doses in Arm 1, which made it difficult to draw conclusions regarding any potential nonlinearities. These preliminary findings supported the conclusion that imalumab exposure at the 25 mg/kg dose in Arm 2 is comparable to the 37.5 mg/kg dose in Arm 1 on C1D1.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

There is limited experience with imalumab administration in humans. Although the repeat-dose toxicology study showed acute or subacute inflammation of the joints of animals, which was deemed related to the administration of imalumab, there were no cases of drug related joint inflammation in the 48 human subjects who had received imalumab doses ranging from 1 to 50 mg/kg IV in the ongoing Phase 1 study as of 2015 JUL 01. In light of these nonclinical and clinical findings, and to proactively assess potential joint toxicity in humans, a physical examination of the joints will be performed at screening and then at regular bimonthly intervals. The DRC will review all safety data with particular attention to pertinent AEs such as allergic reactions and joint pain on a monthly basis.

In general, AEs associated with the administration of monoclonal antibody agents include allergic reactions (eg, hives or itching), influenza-like symptoms, nausea, diarrhea, and skin rashes.

As with any IV protein product, allergic type hypersensitivity reactions are possible. Subjects must be closely monitored and carefully observed for any symptoms throughout the infusion period. Subjects should be informed of the early signs of hypersensitivity reactions and anaphylaxis, including hives, generalized urticaria, tightness of the chest, shortness of breath, wheezing, and hypotension. If any of these symptoms occur, investigational drug administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented. Other rare SAEs may include low blood cell counts, coronary complications, and serious infections (including skin infections).

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this study, in subjects with progressive measurable mCRC, is as follows:

- To evaluate the safety and tolerability of imalumab in combination with 5-FU/LV or panitumumab to determine the recommended phase 2 dose (RP2D) of each combination
- To compare the efficacy of imalumab in combination with 5-FU/LV versus SoC (investigator choice) as third or fourth treatment line in subjects with KRAS mut and/or NRAS mut tumors
- To compare the efficacy of imalumab in combination with panitumumab versus SoC (investigator choice) as third or fourth treatment line in subjects with KRAS wt and NRAS wt tumors

Furthermore, the pharmacokinetic (PK) profile of imalumab in combination with 5-FU/LV or panitumumab will be characterized, and limited pharmacodynamic (PD) serum markers will be explored.

7.2 Primary Objectives

The primary objectives of the study are:

- To determine the RP2D of imalumab in combination with 5-FU/LV or panitumumab (Part 1)
- To compare PFS between imalumab in combination with 5-FU/LV for subjects with KRAS mut and/or NRAS mut tumors or in combination with panitumumab for subjects with KRAS wt and NRAS wt tumors, versus SoC (investigator choice), as third or fourth treatment line (Part 2)

7.3 Secondary Objectives

7.3.1 Efficacy

The secondary efficacy objectives of the study are:

- To compare overall response rate (ORR) and clinical benefit rate (CBR) in subjects treated at RP2D with imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line
- To compare OS of subjects who received imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line

7.3.2 Safety

The secondary safety objective of the study is:

- To assess the safety and tolerability of imalumab in combination with 5-FU/LV or panitumumab

7.3.3 Pharmacokinetics

The secondary PK objective of the study is:

- To characterize the PK of imalumab in combination with 5-FU/LV or panitumumab

7.3.4 Quality of Life

The secondary QoL objective of the study is:

- To compare QoL of subjects who received imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line

7.4 Exploratory Objectives

7.4.1 Pharmacodynamics

The exploratory PD objective of the study is:

- To characterize oxidized macrophage migration inhibitory factor (oxMIF) and total MIF in plasma prior to and during treatment with imalumab in combination with 5-FU/LV or panitumumab

7.4.2 Genetic Biomarkers

The exploratory genetic biomarker objective of the study is:

- To characterize tumor-associated genetic alterations in blood/urine (for all subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for exploratory biomarker analyses)

The sponsor will obtain available historical tumor mutational testing results for subjects.

7.4.3 Quality of Life

The exploratory QoL objective of the study is:

- To compare disease-specific QoL and health utility in subjects treated with imalumab in combination with 5-FU/LV or panitumumab versus SoC (investigator choice) as third or fourth treatment line

8. STUDY DESIGN

8.1 Brief Summary

This open-label, randomized study to be conducted in approximately 40 study sites in the US and EU. The study comprises a Safety Run-in phase (Part 1) with 2 ascending doses of imalumab; and an exploratory phase (Phase 2a, ie, [Part 2]) with a 2-treatment-arm design. Approximately 78 to 90 subjects (approximately 12 to 24 subjects in Part 1 and 66 subjects in Part 2) with measurable mCRC, who have progressed after receiving at least 2, but no more than 3, prior treatment lines including SoC, will be enrolled in the study. Subjects can only participate in either Part 1 or Part 2 of the study. Adjuvant therapy in the metastatic setting (administered following a surgical procedure) and investigational products are included in the definition of a prior line of treatment for the purposes of this study.

In both parts, imalumab will be administered IV QW as part of a 4-week treatment cycle. Antitumor activity will be evaluated by the investigator after completion of every other treatment cycle (ie, every 2 cycles) using magnetic resonance imaging (MRI) or computerized tomography (CT) imaging and in accordance to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Treatment will be continued until disease progression, unacceptable toxicity, withdrawal of consent, or for any other reason as detailed in Section 9.3.

8.2 Overall Study Design

8.2.1 Part I: Safety Run-In

Subjects will be enrolled into 2 sequential cohorts, with a minimum of 3 and a maximum of 6 subjects per cohort. Subjects will receive imalumab at 7.5 and 10 mg/kg QW in combination with infusional 5-FU/LV given Q2W in subjects with KRAS mut and/or NRAS mut tumors, or in combination with panitumumab given Q2W in subjects with KRAS wt and NRAS wt tumors. Treatment will be administered in 4-week cycles and will continue until disease progression, unacceptable toxicity, withdrawal of consent, or for any other reason as detailed in Section 9.3.

The DRC will meet for safety reviews after 3 subjects in a dosing cohort have completed the first treatment cycle (ie, after 28 days) to decide if additional subjects must be enrolled or if the next dose level can be opened. For each combination, based on all data of all evaluable subjects, the DRC will determine the RP2D, or decide if an intermediate dose level must be explored. The RP2D will be used as the dose for Part 2.

See Section 15.4.1 for additional details on the DRC.

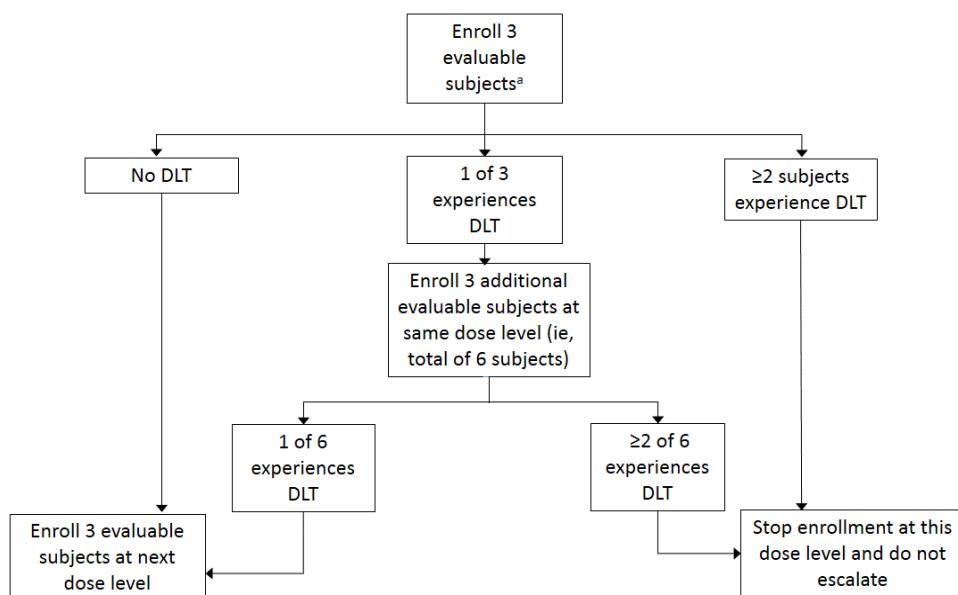
8.2.1.1 Stopping Criteria for Dose Escalation

For each combination, enrollment will proceed according to the following rules based on the occurrence of DLTs:

- If zero out of 3 evaluable subjects experience a DLT during the first 28 days after the first administration of study drug at the first dose level, the second dose level will be opened for enrollment after review of the safety data by the DRC
- If 1 out of 3 evaluable subjects experiences a DLT during the first 28 days after administration of study drug at the first dose level, 3 additional subjects will be enrolled at the first dose level, for a total of 6 evaluable subjects. After review of the safety data of all 6 evaluable subjects, the DRC will decide if the second dose level or a lower dose level will be explored
- If 2 or more evaluable subjects experience a DLT during the first 28 days after the first administration of study drug at the first dose level, the second dose level will not be open to enrollment, and the DRC will decide if a lower dose level will be explored

See Section 8.2.3 for DLT definition. See [Figure 1](#) for a schematic of the dose escalation.

Figure 1
Protocol 391401 Dose Escalation Scheme



Abbreviation: DLT=dose-limiting toxicity.

^a A subject is considered evaluable if he/she can be evaluated for adverse events during the first 28 days after first study drug administration, or is withdrawn from the study due to a DLT.

8.2.2 Part 2: Exploratory Phase 2a

This is a 2-treatment-arm phase using a 2:1 ratio for subjects to receive imalumab + 5-FU/LV or imalumab + panitumumab (Arm A) or SoC per investigator choice (Arm B). Within each stratum, subjects will be randomized in a 2:1 ratio to receive imalumab + 5-FU/LV (KRAS mut and/or NRAS mut tumors) or imalumab + panitumumab (KRAS wt and NRAS wt tumors) (Arm A) or SoC per investigator choice (Arm B). Randomization will occur via an Interactive Response Technology (IRT) System until the targeted number of subjects in each treatment arm is achieved. For each combination in Arm A, subjects will receive imalumab at the RP2D determined in Part 1 for the corresponding combination. Subjects in Arm A with KRAS mut and/or NRAS mut tumors will receive 5-FU/LV in addition to imalumab at the RP2D dose determined in Part 1. Subjects in Arm A with KRAS wt and NRAS wt tumors will receive panitumumab in addition to imalumab at the RP2D dose determined in Part 1. Subjects in Arm B with KRAS/NRAS mut or wt tumors will receive investigator's choice (SoC, including best supportive care). If investigator's choice is to give panitumumab, subjects must have KRAS wt and NRAS wt tumors. All subjects will be treated until disease progression, unacceptable toxicity, or withdrawal of consent.

An independent Data Safety Monitoring Board (DSMB) will review accumulating unblinded safety data of subjects in Part 2 on a quarterly basis. See Section [15.4.2](#) for additional details.

The effect of imalumab in combination with 5-FU/LV or panitumumab on tumor-associated genetic biomarkers will be monitored. Blood and urine samples will be collected from those subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for this optional exploratory analysis. It is possible that blood/urine biomarkers may correlate with clinical outcome (safety and efficacy) in response to imalumab treatment.

8.2.3 Definition of Dose-Limiting Toxicity

A DLT is defined as any drug-related treatment-emergent adverse event (TEAE) (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) that occurs during the first 28 days after treatment start and that meets any of the following criteria:

- Any \geq Grade 3 non-hematologic toxicity excluding:
 - a. Mucositis/stomatitis of Grade 3 that resolves to Grade 1 or less with supportive measures within 7 days
 - b. Diarrhea of < 3 days duration following adequate and optimal therapy

- c. Nausea and vomiting of < 3 days duration with adequate and optimal therapy
- d. Fatigue of < 7 days duration following initiation of adequate supportive care
- e. Alopecia
- f. Any single laboratory value out of the normal range that has no clinical significance and that resolves to \leq Grade 2 with adequate measures within 7 days; transient Grade 3 elevations (lasting < 5 days) of hepatic transaminases in the absence of simultaneous increase in serum bilirubin
- Any Grade 4 hematologic toxicity excluding:
 - a. Grade 4 neutropenia lasting for \leq 5 days and not associated with fever
 - b. Isolated Grade 4 lymphocytopenia without clinical correlate
- Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia associated with bleeding
- Any life-threatening complication or abnormality not covered in the NCI CTCAE v4.03

In subjects treated with panitumumab, if a dermatologic reaction develops that is Grade 3 (NCI CTCAE v.4.03) or higher (or is considered intolerable), the dose modifications recommended in the product label will be implemented.³⁴

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is anticipated to be approximately 21 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be 15 months. Study completion is estimated to occur when 75% of OS events have been reported.

Subject participation includes a maximum of 4 weeks for screening, and 30 (\pm 7) days for post-treatment safety follow-up. Subjects will receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent. For subjects who have stopped study drug or have documented disease progression, post-study telephone calls to assess OS will be made by site staff every 3 months.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary safety outcome measure is the occurrence of DLTs (Part 1).

The primary efficacy outcome measure is PFS defined as time between treatment initiation and tumor progression (per RECIST v1.1 criteria) or death from any cause, with censoring of subjects who are lost to follow-up or withdraw consent (Part 2).

8.4.2 Secondary Outcome Measures

8.4.2.1 Immunogenicity Outcome Measures

- Occurrence of binding and/or neutralizing anti-imalumab antibodies
- Incidence and severity of infusion reactions after imalumab

8.4.2.2 Safety Outcome Measures

- Occurrence of SAEs and/or TEAEs, regardless of causality or relationship to study drug and coded according to NCI CTCAE v4.03
- Other safety measurements: physical or instrumental examinations, electrocardiograms (ECGs), vital signs, and clinically relevant changes in instrumental examinations or laboratory values

8.4.2.3 Efficacy Outcome Measures

- Response evaluation according to RECIST v1.1
- OS, defined as time from randomization to death of any cause

8.4.2.4 Pharmacokinetic Outcome Measures

Imalumab plasma PK will be characterized using a population PK modeling approach, in combination with data from other studies. Results of population PK modeling will be reported in a separate report.

8.4.2.5 Quality of Life Outcome Measures

The QoL outcome measure uses the EORTC QLQ-C30.

8.4.3 Exploratory Outcomes Measure

The exploratory PD outcome measures include plasma levels of oxMIF and total MIF.

Genetic biomarkers will also be investigated as an optional exploratory outcome. Exploratory genetic biomarker outcome measures include tumor-associated genetic alterations of cfDNA in blood/urine, for subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for these analyses. The sponsor will obtain available historical tumor mutational testing results for subjects.

The exploratory QoL outcome measures use the EORTC QLQ for colorectal cancer 29 (EORTC QLQ-CR29) and the European Quality of Life – 5 Dimensions questionnaire (EQ-5D). The EORTC QLQ-CR29 will be used as a supplement to the EORTC QLQ-C30 to assess the disease-specific aspects of colorectal cancer. The EQ-5D is a health utility measure.

8.5 Randomization and Blinding

This is an open-label study. In Part 2, randomization will occur to minimize bias and fulfill a 2:1 ratio between Arm A and Arm B. Prior to randomization, subjects will be stratified according to their KRAS and NRAS mutation status. Randomization will occur via an IRT System until the targeted number of subjects in each treatment-arm is achieved.

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

- Excessive toxicity or clinically meaningful SAE that may pose significant health risks
- Decision by the sponsor to interrupt or terminate the study at any time for reasons including, but not limited to, safety or ethical issues or insufficient non-compliance

When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to its taking effect. The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is interrupted or terminated for safety reasons, and will also inform the regulatory authorities of the interruption or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the interruption or termination.

8.7 Investigational Product and Standard Drugs

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 Imalumab

Dosage Form: Injection, solution

Packaging: Imalumab (50 mg/mL) will be supplied as a ready-for-use, sterile, non-pyrogenic liquid preparation in single-dose glass vials of 5 mL (with acceptable fill variance from 5.45 to 5.85 grams).

Labeling: The product will be labeled according to the valid regulatory requirements for clinical studies.

Storage: Imalumab must be stored under refrigerated conditions (2° to 8°C or 36° to 46°F) in the original package to protect from light. Do not freeze the product. Do not use if expiration date is exceeded or carton is damaged.

8.7.1.2 Leucovorin

Dosage Form: Injection, solution

Packaging: LV will be obtained from a local pharmacy by the study site.

Labeling: LV will be labeled by the manufacturer, and additional labels will be provided by the sponsor to denote investigational usage, if applicable.

Storage: LV must be stored in accordance to the package label.

8.7.1.3 5-Fluorouracil

Dosage Form: Injection, solution

Packaging: 5-FU will be obtained from a local pharmacy by the study site.

Labeling: 5-FU will be labeled by the manufacturer, and additional labels will be provided by the sponsor to denote investigational usage, if applicable.

Storage: 5-FU must be stored in accordance to the package label.

8.7.1.4 Panitumumab

Dosage Form: Injection, solution

Packaging: Commercially available panitumumab will be required for the study and will be sourced locally by the study site. If obtaining supplies is prohibitive, sponsor facilitation may be provided.

Labeling: Panitumumab will bear the label as provided by the manufacturer; however, additional labels will be provided by the sponsor to denote investigational usage, if applicable.

Storage: Panitumumab must be stored in accordance to the package label.

8.7.1.5 Standard of Care (Investigator Choice)

Standard of care drugs will be obtained from a local pharmacy by the study site. The SoC drugs will bear the label as provided by the manufacturer and will **not** be re-labeled at the study site.

8.7.2 Preparation and Storage of Pooled Product

8.7.2.1 Imalumab

Imalumab solution for injection must be prepared on the day of administration. The initial dose (in mg) will be prepared based on the subject's body weight at screening/baseline. Dose (in mg) will be adjusted when a $\geq 10\%$ change in the subject's weight is observed (compared to the body weight currently being used for the basis of dose preparation).

Volume (ml) = [Dose (mg/kg)/Concentration (mg/mL)] x Subject Weight (kg)

Concentration (mg/mL) = 50 mg/mL

Depending on the amount of imalumab to be administered, the content of multiple vials of imalumab may be pooled into a syringe of appropriate size (maximum of 50 mL), and may require more than one syringe to be filled with imalumab.

The vials will be brought to room temperature. The flip cap is then removed from the study drug vial, and the exposed stopper wiped with alcohol. All imalumab preparations for IV injection must be prepared aseptically under a laminar flow hood and should be inspected visually for particulate matter and discoloration. Only clear or slightly opalescent, colorless to yellow to pink solutions without visible particles are to be administered. No dilution of imalumab is permitted. Further details regarding the preparation of imalumab are provided in the Pharmacy Manual.

Once prepared, the imalumab solution for injection will be kept at room temperature or, if not used immediately, at 2° to 8°C (36° to 46°F). For the latter, the imalumab solution must be allowed sufficient time to equilibrate to room temperature prior to administration, noting that infusion of imalumab shall begin within 7 hours (4 hours prior to aspiration and 3 hours after aspiration) from when the vials are removed from storage. Vials removed from storage to equilibrate to room temperature must not be removed from secondary packaging (original outer box), in order to protect product from light until administration.

Administration of imalumab should be performed in accordance with Section 8.7.3.1.

Do not dilute the imalumab solution with any other solutions or IV fluids unless agreed upon by the sponsor.

8.7.2.2 5-Fluorouracil, Leucovorin, and Panitumumab

Fluorouracil, LV, and panitumumab will be reconstituted according to the package label provided by the manufacturers and according to local pharmaceutical regulations.

8.7.2.3 Standard of Care Drugs

Standard of care drugs will be reconstituted according to the package label provided by the manufacturers and according to local pharmaceutical regulations. Investigators will also respect the contraindications in the Summaries of Product Characteristics (SmPCs) of the comparators and give consideration to the special warnings and precautions in the SmPCs of comparators.

8.7.3 Administration

8.7.3.1 Imalumab

For Parts 1 and 2, once the required volume of imalumab is aspirated into a suitably sized syringe, the study drug will be administered via IV infusion at a flow rate between 1.0 and 3.6 mL/min. The syringe may be hand-pushed for IV administration; alternatively, a syringe-driver pump may be used to actuate the syringe depending on the user/administrator's comfort and/or preference. Considerations include: the amount of product to be infused, the size of the syringe used, the length of time to administer the product, and the user's ability to deliver the product as indicated. Parameters, including flow rate, shall be programmed into the pump, after which infusion can begin. While a 50 mL syringe is generally the maximum syringe size that can be loaded into a syringe driver pump, if additional volume is required for the administration, the emptied syringe can be replaced in the pump with a new syringe filled with the additionally required study drug.

8.7.3.2 5-Fluorouracil, Leucovorin, and Panitumumab

For Parts 1 and 2, LV will be administered via IV infusion at a dose of 400 mg/m² over 2 hours. Immediately following LV administration, 5-FU will be administered via IV infusion pump at a dose of 2400 mg/m² over 46 hours.

For Parts 1 and 2, panitumumab will be administered via IV infusion pump at a dose of 6 mg/kg over 60 minutes (maximum of 1000 mg; if >1000 mg, infusion will occur over 90 minutes).

8.7.3.3 Standard of Care Drugs

Standard of care drugs will be selected by the investigator based on individual subjects' needs and clinical disease course. If panitumumab is the selected SoC for subjects in Arm B (control arm), the subjects must not have failed prior therapy with panitumumab or have a known history of keratitis, ulcerative keratitis or severe dry eye. Administration of all SoC drugs should be performed in accordance with the respective product label. Investigators will also respect the contraindications in the SmPCs of the comparators, and give consideration to the special warnings and precautions in the SmPCs of comparators.

8.7.4 Description of Treatment

In both Parts 1 and 2, imalumab administration will occur QW, and 5FU/LV or panitumumab administration will occur Q2W in 4-week cycles. Treatment schedule for SoC drugs will be in accordance with the respective product label.

For all subjects in Parts 1 and 2, treatment will continue until disease progression, excessive toxicity, withdrawal of consent, or for any other reason as detailed in Section 9.3.

8.7.4.1 Part 1: Safety Run-In

Regimen 1:

Imalumab (7.5 or 10 mg/kg) will be administered (as per Section 8.7.3.1) 1 hour before 5-FU/LV (administered as per Section 8.7.3.2).

Regimen 2:

Imalumab (7.5 or 10 mg/kg) will be administered (as per Section 8.7.3.1) 1 hour before panitumumab (administered as per Section 8.7.3.2).

8.7.4.2 Part 2: Exploratory Phase 2a

8.7.4.2.1 Arm A

Imalumab (at the RP2D, as determined in Part 1) will be administered (as per Section 8.7.3.1) 1 hour before 5-FU/LV (administered as per Section 8.7.3.2) in subjects with KRAS mut and/or NRAS mut tumors.

Imalumab (at the RP2D, as determined in Part 1) will be administered (as per Section 8.7.3.1) 1 hour before panitumumab (administered as per Section 8.7.3.2) in subjects with KRAS wt and NRAS wt tumors.

8.7.4.2.2 Arm B (Investigator Choice)

Standard of care will be chosen by the investigator and will be administered according to product label(s) and in accordance to local pharmaceutical regulations. If panitumumab is chosen, it will be administered as described in Section [8.7.3.2](#) and only in subjects with KRAS wt and NRAS wt tumors and in subjects who have not had prior therapy with panitumumab, or have a known history of keratitis, ulcerative keratitis or severe dry eye.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center or home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

In this trial, no source data will be entered directly onto the case report forms (CRFs).

For additional information on study documentation and CRFs, see Section [17.2](#).

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Provision of a signed informed consent
2. Male and female subjects 18 years of age and older at the time of screening
3. Subjects who progressed after receiving at least 2, but no more than 3, prior cancer drug therapy treatment lines including SoC in the metastatic setting
4. Anticipated life expectancy >3 months at the time of screening
5. Weight between 40 kg and 180 kg
6. Histologically or cytologically confirmed diagnosis of CRC
7. Metastatic CRC not amenable to surgical resection
8. Known KRAS, NRAS mutation status (if unknown status for either of these genes, and no archival tissue is available, a fresh tumor biopsy will be obtained)
9. At least 1 measurable lesion as defined by RECIST v1.1
10. ECOG PS of 0-2
11. Adequate hematological function, defined as:
 - a. Platelet count \geq 100,000/ μ L
 - b. Prothrombin time and activated partial thromboplastin time (aPTT) $<$ 1.5 times the upper limit of normal (ULN)
 - c. Absolute neutrophil count (ANC) \geq 1000/ μ L
 - d. Hemoglobin \geq 9 g/dL, without the need for transfusion in the 2 weeks prior to screening
12. Adequate renal function, defined as serum creatinine \leq 2.0 times ULN and creatinine clearance $>$ 50 mL/min or estimated glomerular filtration rate $>$ 50 mL/min/1.73 m²
13. Adequate liver function, defined as:
 - a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) \leq 2.5 times ULN for subjects without liver metastases, or \leq 5 times ULN in the presence of liver metastases
 - b. Bilirubin \leq 2.0 times ULN, unless subject has known Gilbert's syndrome
14. Adequate venous access

15. For female subjects of childbearing potential, the subject presents with a negative serum pregnancy test at screening and agrees to employ 2 forms of adequate birth control measures, including at least 1 barrier method (eg, diaphragm with spermicidal jelly or foam, or [for male partner] condom) throughout the course of the study and for at least 90 days after the last administration of imalumab. In addition, these birth control methods must be continued for at least 180 days after last administration of 5-FU in subjects who receive this treatment. Secondary contraceptive measures could be either birth control pills, patches, or intrauterine devices
16. For male subjects, they must agree to use adequate contraceptive measures including at least 1 barrier method (eg, condom with spermicidal jelly or foam and [for the female partner] diaphragm with spermicidal jelly or foam, birth control pills/patches, or intrauterine device) and abstain from sperm donation throughout the course of the study and for at least 90 days after the last administration of imalumab. In addition, these birth control methods must be continued for at least 180 days after last administration of 5-FU in subjects who receive this treatment
17. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known central nervous system metastases
2. Prior malignancy(s) within the past 3 years, with the exception of curatively treated basal or squamous cell carcinoma of the skin, locally advanced prostate cancer, ductal carcinoma in situ of breast, in situ cervical carcinoma and superficial bladder cancer
3. Prior treatment with panitumumab for subjects with KRAS wt and NRAS wt tumors
4. Known history of keratitis, ulcerative keratitis, or severe dry eye in subjects with KRAS wt and NRAS wt tumors
5. Residual AE from previous treatment > Grade 1, except neuropathy and alopecia
6. Prior intolerance to fluoropyrimidine for subjects with KRAS mut and/or NRAS mut tumors

7. Myocardial infarction within 6 months prior to C1D1, and/or prior diagnoses of congestive heart failure (New York Heart Association Class III or IV), unstable angina, unstable cardiac arrhythmia requiring medication; and/or the subject is at risk for polymorphic ventricular tachycardia (eg, hypokalemia, family history, or long QT syndrome)
8. Uncontrolled hypertension, defined as systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 100 mmHg confirmed upon repeated measures
9. LVEF $<$ 40% as determined by echocardiogram (ECHO)/multigated acquisition scan (MUGA) performed at screening or within 90 days prior to C1D1
10. QT/QTc interval $>$ 450 msec, as determined by screening ECG performed no earlier than 1 week before C1D1
11. Prior anti-tumor therapy (chemotherapy, radiotherapy, antibody therapy, molecular targeted therapy, retinoid therapy or hormonal therapy) within 4 weeks ($<$ 28 days) prior to C1D1
12. Major surgery within 4 weeks ($<$ 28 days) prior to C1D1
13. Active joint inflammation or history of inflammatory arthritis or other immune disorder involving joints (osteoarthritis is not exclusionary)
14. Active infection involving IV antibiotics within 2 weeks prior to C1D1
15. Known history of or active hepatitis B virus (HBV) and/or hepatitis C virus (HCV), or active tuberculosis
16. Known history of human immunodeficiency virus (HIV) type 1/2 or other immunodeficiency disease
17. Subject has received a live vaccine within 4 weeks ($<$ 28 days) prior to C1D1
18. Known hypersensitivity to any component of recombinant protein production by CHO cells
19. Exposure to an investigational product or investigational device in another clinical study within 4 weeks ($<$ 28 days) prior to C1D1, or is scheduled to participate in another clinical study involving an investigational product or device during the course of this study
20. Subject is breastfeeding or intends to begin breastfeeding during the course of the study
21. Any disorder or disease, or clinically significant abnormality on laboratory or other clinical test(s) (eg, blood tests, ECG), that in medical judgment of the investigator may impede the subject's participation in the study, pose increased risk to the subject, and/or confound the results of the study
22. Subject is a family member or employee of the investigator

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.3.3.8 and Section 20.2.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- Disease progression according to RECIST v1.1
- Clinical progression due to the subject's underlying malignancy
- Excessive toxicity
- Intercurrent illness unrelated to the subject's underlying malignancy that prevents further participation
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
- The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
- Participation in another clinical study involving an investigational product during the course of the study.
- Protocol non-compliance
- Subject withdrawal of consent
- Study closure or termination by the sponsor
- Use of prohibited therapies (see protocol Section 10.4)

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any subject who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The SIC will comprise the following series of numbers: protocol identifier (eg, 391401) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor, and 3- or 4-digit subject number (eg, 0003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 391401-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) will be permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC, and new CRF will be required for that subject. At re-screening, results from assessments that were conducted within the previous 21 days can be reused, to avoid repetition of numerous Screening assessments.

The overall study design is illustrated in [Figure 2](#). Details on the procedures to be performed at each study visit, including screening, can be found in [Supplement 20.2, Schedule of Study Procedures and Assessments](#).

10.3.1 Screening Assessments

After informed consent has been obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in [Section 9.1](#) and [Section 9.2](#), respectively. Screening procedures must be performed within 28 days prior to first imalumab administration (C1D1).

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria and completion of the required eligibility form)
- Demographics (date of birth, gender, race, and ethnicity)
- Relevant medical and surgical history
- Vital signs (body temperature, heart rate, blood pressure, respiratory rate, and weight)
- Physical examination
- ECOG PS
- 12-lead ECG
- ECHO/MUGA
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation)
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Genetic testing (for KRAS and NRAS tumor status)
- CT or MRI scans for tumor measurement (as assessed by RECIST v1.1), unless results from CT or MRI scans performed within 28 days prior to first imalumab administration (C1D1), are available
- Blood sample for immunogenicity (anti-drug antibody [ADA] and neutralizing anti-drug antibody [NADA])
- Blood sample for PK assessment
- Blood sample for PD biomarkers (oxMIF and total MIF)
- Blood sample for cfDNA (genetic biomarkers)
- Urine sample for cfDNA (genetic biomarkers)
- Collection of AEs
- Review of concomitant medications/non-drug therapies
- Entry into IRT System

See the Schedule of Study Procedures and Assessments ([Table 3](#)) for additional details on screening assessments.

10.3.2 Baseline Assessments (Cycle 1 Day 1, Predose)

At the baseline visit (C1D1), subject eligibility will be confirmed and all questionnaires will be completed prior to the start of any assessments. The following baseline assessments will be performed for all subjects prior to dosing:

- EORTC QLQ-C30
- EORTC QLQ-CR29
- EQ-5D
- Vital signs (body temperature, heart rate, blood pressure, respiratory rate, weight, and height; recorded within 30 minutes prior to start of treatment)
- Physical examination
- ECOG PS
- 12-lead ECG
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation). Immediately prior to Cycle 1, laboratory assessments can be performed either on Day -1 or on Day 1 predose
- Urine dipstick test for women of childbearing potential
- Urinalysis
- For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are to be collected **at any time on Day 1 prior to infusion** (see [Table 6](#)).
- Collection of AEs
- Review of concomitant medications/non-drug therapies
- Entry into IRT System for randomization

See the Schedules of Study Procedures and Assessments ([Table 3](#), [Table 4](#), and [Table 5](#)) for additional details on baseline (Day 1, predose) assessments.

10.3.3 Treatment Cycles

After all baseline assessments have been completed, subjects will begin treatment Cycle 1 with administration of their first dose of imalumab. Subjects will receive imalumab QW on Days 1, 8, 15, and 22 as part of a 4-week/28-day treatment cycle. A new cycle should begin after every 28-day period (ie, 4 weeks). For all subjects, treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or for any other reason as detailed in Section [9.3](#).

10.3.3.1 Study Drug Administration

All study drug administrations will take place at the study site or a qualified facility with medical supervision (such as an infusion center) where a subject's safety can be monitored during and following administration. All study drugs must be administered by a qualified healthcare professional (see Section [8.7.3](#) for additional details).

At any time during the study, any of the study drugs may be interrupted or discontinued at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. If treatment with 5-FU/LV or panitumumab is interrupted due to an AE, and there are no concurrent safety concerns regarding imalumab, treatment with imalumab may be continued while treatment with 5-FU/LV or panitumumab is interrupted.

No dose modification is planned for this study, with the exception of the dose modifications referred to in Section [8.2.3](#) for subjects treated with panitumumab who develop dermatologic reactions Grade 3 (CTCAE v.4.03) or higher, or considered intolerable.

Any injection site reactions, regardless of causality, will be recorded on the AE CRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate CRF.

The use of an indwelling catheter to withdraw blood samples is permitted, in particular on the days of intensive blood sampling. When blood sample collection occurs within 24 hours following study drug administration, the blood sample should not be collected from the same side used for study drug injection.

All study drugs should be prepared on the day of administration, as described in Section [8.7.2](#) and Section [8.7.3](#).

For each study drug administration, the following information will be captured in the appropriate CRF(s):

- Planned dose
- Date and start and end times of imalumab injection
- Actual volume injected
- Time of interruption, restart, or discontinuation, as applicable
- Volume injected at the time of interruption or discontinuation, as applicable
- Reason(s) for interruption or discontinuation, if applicable
- Any AE(s), if applicable

- Use of any medications/non-drug therapies including those used to treat AE(s), if applicable.

10.3.3.1.1 Imalumab Administration

Considering the limited experience of imalumab in humans at the time of this study's commencement, subjects should remain on-site for at least 8 hours following the first imalumab administration, for safety monitoring with medical supervision. During the Safety Run-in, subjects should remain on-site for safety monitoring for at least 2 hours following imalumab administration on Day 8 and Day 15 of Cycle 1 (applicable to all subjects).

Injection-related reactions that have been observed with other monoclonal antibodies administered by IV injection include: allergic reactions (eg, hives or itching), influenza-like symptoms, nausea, diarrhea, and skin rashes. Injection-related reactions should be managed according to guidance provided in [Table 1](#).

Table 1 Study 391401: Management of Imalumab Injection-Related Reactions	
NCI CTCAE Grade	Guidance for Management of Reaction
Grade 1 (Mild, transient reactions not requiring treatment with medication)	The injection may be interrupted until resolution of symptoms at the discretion of the investigator. If the injection is interrupted, upon symptom resolution the injection may be resumed as tolerated.
Grade 2 (Prolonged response or recurrence after symptomatic medication)	The injection is to be interrupted, and treatment with symptomatic medications initiated (eg, antihistamines, antipyretics, narcotics, IV fluids). Upon resolution of symptoms, the injection may be resumed at the discretion of the investigator.
Grade 3 (Not rapidly responsive to symptomatic medications; subject is hospitalized)	Imalumab administration is to be discontinued, and the subject should be administered best supportive care. In addition, the investigator should contact the sponsor to discuss appropriate follow-up testing.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	

Abbreviations: IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

A kit containing supplies suitable for emergency treatment of anaphylactic reactions and personnel with appropriate expertise/training in administering basic life support and in the management of hypersensitivity reactions must be readily accessible on-site during all imalumab administrations.

10.3.3.1.2 5-Fluorouracil, Leucovorin, Panitumumab, and Standard of Care Administration

Treatments will be administered in accordance with the respective drug's product label. If panitumumab is the selected SoC for subjects in Arm B (control arm), the subjects must not have had prior therapy with panitumumab or have a known history of keratitis, ulcerative keratitis or severe dry eye. Investigators should advise subjects to minimize their exposure to ultraviolet light (sunlight) following treatment with 5-FU or panitumumab.

10.3.3.2 Day 1 of Each Cycle

On Day 1 of each treatment cycle in both Parts 1 and 2 of the study (unless otherwise depicted below), the assessments/treatment administrations listed below will occur. At baseline, ie, C1D1, the predose assessments described in Section [10.3.2](#) should be conducted before proceeding with the first administration of study drug.

Prior to administration of study drug:

- Vital signs (including body temperature, heart rate, blood pressure, respiratory rate, and weight; recorded within 30 minutes prior to start of treatment)
- Physical examination
- ECOG PS
- 12-lead ECG
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation)
- Urine dipstick test for women of childbearing potential
- Urinalysis
- For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are to be collected **-2 to 0 h predose** (see [Table 6](#)).
- Collection of AEs
- Review of concomitant medications/non-drug therapies
- Entry into IRT System (Part 1: all subject visits; Part 2: Arm A subject visits only)

Administration of study treatment(s):

- Imalumab administration:
 - Part 1: all subjects
 - Part 2: subjects in Arm A

- 5-FU/LV or panitumumab administration:
 - Part 1: Subjects with KRAS mut and/or NRAS mut tumors will receive 5-FU/LV, and subjects with KRAS wt and NRAS wt tumors will receive panitumumab.
 - Part 2: In Arm A (5-FU/LV), subjects with KRAS mut and/or NRAS mut tumors will receive 5-FU/LV, and subjects with KRAS wt and NRAS wt tumors will receive panitumumab.
- SoC administration:
 - Part 2, Arm B: For SoC, drug dose and schedule to be given in accordance with product label.

Following administration of study treatment:

- On Day 1 of each cycle:
 - Vital signs measurement should be recorded within 30 minutes of completion of the imalumab injection
- On Day 1 of first cycle only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected at **0 to 2 h postdose** and **6 to 8 h postdose** (see [Table 6](#)).
 - 12-lead ECG, 2 (± 1) h postdose
 - Following the first imalumab administration, subjects should remain at the study site for at least 8 hours, for safety monitoring with medical supervision. Upon leaving the site following the first imalumab administration, subjects should remain in close proximity to medical care until completion of the Day 2 study visit.
- On Day 1 of each subsequent treatment cycle:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected at **0 to 2 h postdose** (see [Table 6](#)).
- On Day 2 or Day 4 of first cycle only:
 - On Day 2 (**24 \pm 4 h post first dose**) **OR** Day 4 (**72 \pm 8 h post first dose**): blood draw for the determination of levels of free oxMIF and free total MIF (see [Table 6](#))

10.3.3.3 Day 8 of Each Cycle

On Day 8 of each treatment cycle in both Parts 1 and 2 of the study (unless otherwise depicted below), the following assessments/treatment administrations will occur:

Prior to administration of study drug:

- Vital signs (including body temperature, heart rate, blood pressure, respiratory rate, and weight; recorded within 30 minutes prior to start of treatment)
- Clinical laboratory assessments:
 - Cycle 1 only: hematology, serum chemistry, and coagulation
 - All subsequent cycles: hematology
- Collection of AEs
- Review of concomitant medications/ non-drug therapies
- Entry into IRT System (Part 1: all subject visits; Part 2: Arm A subject visits only)
- On Day 8 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **-2 to 0 h predose** (see [Table 6](#)).

Administration of study treatment(s):

- Imalumab administration:
 - Part 1: all subjects
 - Part 2: subjects in Arm A
- SoC administration (if applicable):
 - Part 2, Arm B: For SoC, drug dose and schedule to be given in accordance with product label.

Following administration of study treatment:

- Vital signs measurement should be recorded within 30 minutes of completion of the imalumab injection
- On Day 8 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **0 to 2 h postdose** (see [Table 6](#)).

10.3.3.4 Day 15 of Each Cycle

On Day 15 of each treatment cycle in both Parts 1 and 2 of the study (unless otherwise depicted below), the following assessments/treatment administrations will occur:

Prior to administration of study drug:

- Vital signs (including body temperature, heart rate, blood pressure, respiratory rate, and weight; recorded within 30 minutes prior to start of treatment)
- Physical examination
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation)
- Collection of AEs
- Review of concomitant medications/ non-drug therapies
- Entry into IRT System (Part 1: all subject visits; Part 2: Arm A subject visits only)
- On Day 15 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **-2 to 0 h predose** (see [Table 6](#)).

Administration of study treatment(s):

- Imalumab administration:
 - Part 1: all subjects
 - Part 2: subjects in Arm A
- 5-FU/LV or panitumumab administration:
 - Part 1: Subjects with KRAS mut and/or NRAS mut tumors will receive 5-FU/LV, and subjects with KRAS wt and NRAS wt tumors will receive panitumumab.
 - Part 2: In Arm A (5-FU/LV), subjects with KRAS mut and/or NRAS mut tumors will receive 5-FU/LV, and subjects with KRAS wt and NRAS wt tumors will receive panitumumab
- SoC administration (if applicable)
 - Part 2, Arm B: For SoC, drug dose and schedule to be given in accordance with product label.

Following administration of study treatment:

- Vital sign measurements should be recorded within 30 minutes of completion of the imalumab injection
- On Day 15 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **0 to 2 h postdose** (see [Table 6](#)).

10.3.3.5 Day 22 of Each Cycle

On Day 22 of each treatment cycle in both Parts 1 and 2 of the study (unless otherwise depicted below), the following assessments/treatment administrations will occur:

Prior to administration of study drug:

- Vital signs (including body temperature, heart rate, blood pressure, respiratory rate, and weight; recorded within 30 minutes prior to start of treatment)
- Clinical laboratory assessments (hematology only)
- Collection of AEs
- Review of concomitant medications/ non-drug therapies
- Entry into IRT System (Part 1: all subject visits; Part 2: Arm A subject visits only)
- On Day 22 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **-2 to 0 h predose** (see [Table 6](#)).

Administration of study treatment(s):

- Imalumab administration:
 - Part 1: all subjects
 - Part 2: subjects in Arm A
- SoC administration (if applicable, for subjects receiving 4-week treatment cycles only):
 - Part 2, Arm B: For SoC, drug dose and schedule to be given in accordance with product label.

Following administration of study treatment:

- Vital sign measurements should be recorded within 30 minutes of completion of the imalumab injection
- On Day 22 of Cycle 1 only:
 - For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) are collected **0 to 2 h postdose** (see [Table 6](#)).

10.3.3.6 Day 28 (Cycle 1 and then Every Other Cycle)

- Blood sample for cfDNA (genetic biomarkers)
- Urine sample for cfDNA (genetic biomarkers)

Blood/urine samples will be collected according to the schedule outlined in [Table 3](#), from those subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for this optional exploratory analysis. This sampling will start on in Cycle 1 (Day 28) and will then be repeated every other cycle, ie, Cycle 3 (Day 28), Cycle 5 (Day 28), Cycle 7 (Day 28), etc.

10.3.3.7 Day 28 (Cycle 2 and then Every Other Cycle)

- CT or MRI scans for tumor measurement (as assessed by RECIST v1.1)

During treatment, scans will be conducted from Cycle 2 (Day 28) and then be repeated every other cycle, ie, Cycle 4 (Day 28), Cycle 6 (Day 28), etc. Tumor measurements by CT or MRI scans will be conducted every 8 weeks in subjects receiving SoC in 3-weekly treatment cycles (the study day of this assessment will vary from cycle to cycle; see [Table 5](#)).

10.3.3.8 End of Study/Early Termination Visit

Subjects who experience disease progression or who discontinue early from the study will be asked to undergo an End of Study/Early Termination visit. All questionnaires will be completed prior to the start of any assessments.

The following assessments will be performed at this visit:

- EORTC QLQ-C30
- EORTC QLQ-CR29
- EQ-5D
- Vital signs (body temperature, heart rate, blood pressure, respiratory rate, and weight)
- Physical examination
- ECOG PS
- 12-lead ECG
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation)
- Urine dipstick test for women of childbearing potential
- Urinalysis
- CT or MRI scans for tumor measurement (as assessed by RECIST v1.1), if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit.

- For subjects treated with imalumab, blood sample for immunogenicity (ADA and NADA)
- For subjects treated with imalumab, blood sample for cfDNA (genetic biomarkers)
- For subjects treated with imalumab, urine sample for cfDNA (genetic biomarkers)
- Collection of AEs
- Review of concomitant medications/non-drug therapies
- Entry into IRT System

10.3.3.9 Safety Follow-Up Visit

Following the End of Study/Early Termination visit, subjects will undergo a Safety Follow-up visit within 30 (± 7) days after the last dose of study treatment. All questionnaires will be completed prior to the start of any assessments. The following assessments will be performed at this visit:

- EORTC QLQ-C30
- EORTC QLQ-CR29
- EQ-5D
- Vital signs (body temperature, heart rate, blood pressure, respiratory rate, and weight)
- Physical examination
- ECOG PS
- 12-lead ECG
- Clinical laboratory assessments (hematology, serum chemistry, and coagulation)
- Urine dipstick test for women of childbearing potential
- Urinalysis
- If no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan, CT or MRI scan for tumor measurement as assessed by RECIST v1.1
- For subjects treated with imalumab, blood sample for immunogenicity (ADA and NADA)
- Collection of AEs
- Review of concomitant medications/non-drug therapies

10.3.3.10 Survival Follow-Up (Post Therapy)

For subjects who have stopped study drug or have documented disease progression, post-study telephone calls to assess OS will be made by site staff every 3 months.

10.4 Medications and Non-Drug Therapies

During the study, subjects are expected to be on concomitant medication(s) if they are given treatment for any underlying medical conditions, provided the medications are not anticancer therapies. Subjects may take additional concomitant medication(s) as needed for medical management during this study. If growth factor medications are to be administered, they should be used in accordance with local best practice. All concomitant medication use should be recorded.

The following medications and non-drug therapies are **not** permitted within 4 weeks (< 28 days) prior to study drug administration and during the course of the study:

- Medications:
 - Antitumor therapy, including chemotherapy, radiotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, or hormonal therapy
 - Brivudin, sorivudine, and other nucleoside analogues must be avoided in subjects who receive treatment with 5-FU
 - Live vaccines must be avoided for 6 weeks following last dose of imalumab
 - Other investigational product
- Non-drug therapies:
 - Major surgery
 - Investigational device

The following medications are **not** permitted within 4 weeks (< 28 days) prior to C1D1 and during the course of the study:

- Live vaccines

A subject who has taken any of these medications or received any of these non-drug therapies must be discontinued.

10.5 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion or discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Section 20.2 Schedule of Study Procedures and Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.6 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND GENETIC TESTING

11.1 Plasma Imalumab, oxMIF, and Total MIF

Blood samples (8 mL per sample) for the assessment of plasma imalumab concentrations, oxMIF levels, and total MIF levels in systemic circulation will be prepared from blood

collected into tubes containing sodium citrate (anticoagulant) according to the schedule detailed in Section 10.3 and Table 3. A total of 10 samples (80 mL of blood in total) will be collected in Cycle 1, and 2 samples (16 mL of blood in total) will be collected in each subsequent cycle, from each subject for these measurements. When blood sample collection occurs within 24 hours following imalumab administration, the blood sample should not be collected from the same arm used for imalumab injection. Blood samples are to be processed according to directions provided in the laboratory manual. Each plasma sample (approximately 1 mL each for imalumab PK, oxMIF, and total MIF) will be split into duplicate aliquots.

The exact date and clock time of collection of each blood sample should be collected on the electronic case report form (eCRF). Additionally, the exact date and time, and relevant dosing details of each imalumab dose administered during Cycle 1 should be collected on the eCRF.

11.2 Antitumor Effect – Solid Tumors

In this study, tumor response will be evaluated using RECIST v1.1. Tumor measurements are to be obtained for objective tumor assessment at baseline and on Day 28 of every second treatment cycle (ie, every 8 weeks), as detailed in Section 10.3, Table 3 and Table 4. Tumor measurements by CT or MRI scans will be conducted every 8 weeks in subjects receiving SoC in 3-weekly treatment cycles (the study day of this assessment will vary from cycle to cycle; see Table 5). A tumor measurement should be obtained at the End of Study/Early Termination visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit. A tumor measurement should be obtained at the Safety Follow-up visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan.

For an individual subject, the method (CT and/or MRI scan) used to measure tumor burden at baseline should be used for each subsequent tumor assessment. Baseline tumor measurements and identification of target lesions may be based on imaging obtained within 28 days prior to first imalumab administration (C1D1). Scheduled tumor response assessments must be interpreted prior to the start of the next treatment cycle. A subject's best overall response will be determined at the End of Study/Early Termination Visit.

11.3 Genetic Testing

Genetic testing for KRAS/NRAS mutation status will be performed at screening. If not readily available, genetic testing for KRAS/NRAS mutation status needs to be done early

enough to allow randomization within 4 weeks. If KRAS mutation status is known, the subject can start treatment while NRAS testing is pending.

Dosing regimen for Part 1 is dependent on KRAS/NRAS mutation status. Subjects who are determined to have tumors with KRAS mut, NRAS mut, or both mutations will be assigned to the combination therapy of 5-FU/LV and imalumab. Subjects who are determined to have KRAS wt and NRAS wt tumors will be assigned to the combination therapy of panitumumab and imalumab.

In Part 2 of the trial, subjects will be stratified according to their KRAS/NRAS mutation status and then randomized to Arms A or B in a 2:1 ratio.

11.4 Tumor-Associated Biomarkers

Tumor-associated genetic alterations in blood and urine (for subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for optional exploratory biomarker analyses) will be assessed. Genetic changes of cfDNA using whole exome sequencing, targeted NGS strategy or qPCR on a bi-monthly basis will at least cover the genes, such as but not limited to, KRAS, NRAS, APC, p53, BRAF, PIK3CA, since mutations in these genes have been identified as driver mutations in mCRC and/or are responsible for resistance to anti-EGFR therapy. However, in order to identify imalumab-specific patterns of genetic tumor adaption, a larger panel of cancer-related genes will be analyzed.

Blood samples (10 mL) and urine samples (30 mL) for the assessment of genetic biomarkers (cfDNA) will be collected according to the schedule presented in [Table 3](#). Blood and urine samples are to be processed and frozen according to directions provided in the separate laboratory manual. The exact date and clock time of collection of each blood and urine sample should be collected on the eCRF.

The sponsor will obtain available historical tumor mutational testing results for subjects.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), intercurrent disease (eg,

peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

Each Grade 3 or Grade 4 abnormal laboratory value will be reported as an AE, unless the abnormal value relates to a diagnosis that is itself recorded as an AE or has no clinical correlate.

Events relating to clinical deterioration due to disease progression as a result of the underlying malignancy are not to be considered or analyzed as AEs (or SAEs), but will be recorded on the CRF.

A TEAE is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above

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 dependence or drug abuse
- Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), HBV, HCV, hepatitis E virus (HEV), or parvovirus B19 (B19V)
- Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI) (eg, IB, package insert). The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

For the purposes of this study, all AEs experienced by a subject, including unexpected AEs, will be recorded on the AE CRF.

12.1.1.5 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before first exposure to IP will be recorded on the AE CRF; however, these events will not be considered as AEs and will not be included in the analysis of AEs.

Each TEAE (non-serious AE or SAE) from the first IP exposure until study completion/discontinuation or 30 days (± 7 days) following the last IP treatment will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2.

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the last IP administration, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing [any dose that is at least 20% higher than the highest explored dose level], underdosing [any dose that is lower than the intended explored dose level by 10%], abuse, and withdrawal [see

Section 9.3]), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy of the subject or partner that is confirmed within 90 days after administration of imalumab will be reported on a Pregnancy Form and followed up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided Serious Adverse Event Report (SAER) Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the NCI CTCAE v4.03. In the event an AE is not described in the NCI CTCAE v4.03, the severity grades will be mapped to the following terms:

Table 2 Mapping Conventions for AE Severity (For AEs Not Described Within NCI CTCAE)	
NCI CTCAE Grade	Corresponding AE Severity (if Not Provided in NCI CTCAE)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviations: AE=adverse event; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
 - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
 - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology)
- Unlikely related (either 1 or both circumstances are met)
 - Has little or no temporal relationship to the IP
 - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
 - Follows a reasonable temporal relationship to the administration of IP
 - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
 - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
 - Reappearance of a similar reaction upon re-administration (positive rechallenge)
 - Positive results in a drug sensitivity test (skin test, etc.)
 - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
- Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedules of Study Procedures and Assessments (see [Table 3](#), [Table 4](#), and [Table 5](#)) and Section [12.1.2](#).

Adverse events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. Once the SAE has been recorded in the EDC system, the sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAER Form to meet the 24 hour timeline requirement (for contacts and instructions refer to the SAER Form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAER Form on the applicable eCRF pages.

The reported event will contain as much available information concerning the SAE to enable the sponsor or designee to file a report, which satisfies regulatory reporting requirements. The initial SAE information reported on the applicable eCRF pages (or back-up SAER Form, if applicable) must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
 - Date of onset
 - (S)AE treatment (drug, dose, route of administration)
 - Causal relationship by the Investigator
 - Measures taken (ie, action taken regarding investigational product in direct relationship to the AE)
 - Outcome
- Seriousness criteria (ie, death, life-threatening, or other criterion)

- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAER Forms)

The serious adverse event reporting contact information is provided below by country:

Country	Telephone	Fax
Germany	PPD	PPD
Spain	PPD	PPD
United Kingdom	PPD	PPD
United States	PPD	PPD

Criteria for documenting the relationship to the investigational product, severity, and outcome will be as described in Section 12.1.

All SAEs that are spontaneously reported within 30 days of a subject's last visit are to be collected and reported as previously described.

In medical emergencies, the investigator should use medical judgment and remove the subject from the immediate hazard. The sponsor or designee will be notified regarding the type of emergency and course of action taken and the procedures for SAE reporting will be followed, if necessary.

During a subject's participation in the study, the investigator or institution will provide adequate medical care for any AEs, including clinically significant laboratory values related to the study. The investigator or institution should inform a subject when medical care is needed for an intercurrent illness (clinic, laboratory results, or otherwise) that in the opinion of the investigator should receive medical follow-up.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm.

Urgent safety measures may be taken by the sponsor or clinical investigator and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) and the relevant competent authorities are notified (in writing, if applicable) of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF (and SAER Form if eCRF is not available). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components

- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems, including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 3, Table 4, and Table 5), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. An examination of all major joints will also be performed. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with

differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

In addition, a serum pregnancy test will be performed on women of childbearing potential at screening.

The clinical chemistry panel will consist of sodium, potassium, calcium, magnesium, albumin, ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, creatinine clearance according to Cockcroft-Gault, C-reactive protein, and glucose.

The coagulation panel will include International Normalized Ratio (INR) and aPTT.

Blood will be obtained for assessment of hematology and clinical chemistry parameters according to the schedule detailed in Section 10.3 (see [Table 3](#), [Table 4](#), and [Table 5](#)). Blood volumes obtained are detailed in [Table 7](#). Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at a local laboratory.

12.7.2 Urinalysis

The urinalysis panel will consist of protein, glucose, and blood.

In addition, pregnancy urine dipstick tests for females of childbearing potential will be performed on Day 1 of each treatment cycle (prior to dosing) and at the End of Study/Early Termination visit and Safety Follow-up visit.

Urine will be collected according to the schedule detailed in Section 10.3 (see [Table 3](#), [Table 4](#), and [Table 5](#)).

12.7.2.1 Assessment of Laboratory Values

12.7.2.1.1 Toxicity Grading Scale

Laboratory values will be evaluated according to the NCI CTCAE v4.03.

12.7.2.1.2 Assessment of Abnormal Laboratory Values

Each Grade 3 or Grade 4 abnormal laboratory value will be reported as an AE, unless the abnormal value is a symptom of, or relates to, a diagnosis that is itself recorded as an AE.

For each other abnormal laboratory value, clinically significant values that are treatment-emergent or that are present at baseline and significantly worsen during the study, in the judgment of the investigator, will be reported as AEs. However, clinically significant

abnormal laboratory values will not be reported as AEs if they meet either or both of the following criteria:

1. Value is associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition.
2. Value is associated with a preexisting condition that has not worsened.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (inches or cm) will be measured once at baseline. Weight (lb or kg) will also be collected once at each visit, prior to study drug administration.

Vital signs are to be measured after a 5-minute rest. Sitting position is recommended for blood pressure measurement. Vital signs will be measured according to the schedule described in Section 10.3 (see [Table 3](#), [Table 4](#), and [Table 5](#)).

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis [preferably], symptom, or sign on the AE CRF).

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Electrocardiograms

A 12-lead ECG will be performed at study visits according to the schedule described in Section 10.3 (see [Table 3](#), [Table 4](#), and [Table 5](#)).

Corrected QT (QTc) is to be calculated using Fridericia's formula (where RR = 60/heart rate):

$$QTc = QT/(3\sqrt{RR})$$

Electrocardiograms performed at regular study visits will be interpreted locally.

13. STATISTICS

13.1 Sample Size and Power Calculations

The final sample size of the Safety Run-in (Part 1) is dependent on the pre-stated rules for dose escalation (see Section 8.2.1). In Part 1, the sample size for each dosing regimen (ie, imalumab + 5-FU/LV and imalumab + panitumumab) is expected to be between 6 and 12 subjects (ie, 3 to 6 subjects at each imalumab dose level). Non-evaluable subjects will be replaced to meet study objectives.

The sample size of the exploratory Phase 2a (Part 2) is estimated to be a total of 66 subjects. Assuming that the median PFS is 2.4 months in the control arm and 4.25 months in the experimental arm (hazard ratio 0.565), and using a one-sided α of 0.15 and β of 0.20 with a drop-out rate of 20% at 6 months, 48 PFS events are needed. With an enrollment ratio of 2:1, and taking into account the time for accrual of 1 year and an additional follow-up period of 6 months after the last subject is enrolled, the sample size needed is a total of 44 subjects in the imalumab-containing treatment arms and 22 subjects in the control arm (SoC), for a total of 66 subjects.

13.2 Datasets and Analysis Cohorts

The Safety Population is defined as all subjects who receive at least 1 administration of IP. The Safety Population will be used for all safety analyses in the trial.

The Full Analysis Set (FAS) will serve as the population for the analyses of efficacy data in the trial. The FAS will include all subjects who 1) received at least 1 administration of IP, and 2) have 1 post-baseline tumor response assessment based on RECIST v1.1 or died within 18 weeks of the start of treatment.

13.3 Handling of Missing, Unused, and Spurious Data

For time-to-event type of endpoint, subjects will be censored if lost to follow-up. For all other analysis, only subjects for whom data are available will be included in the statistical analysis. No imputations will be carried out on missing values.

13.4 Methods of Analysis

13.4.1 General Considerations

In general, descriptive summaries will be presented for the safety and immunogenicity variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables, Kaplan-Meier (KM) plots, median time-to-event, and other percentiles will be presented. For the purposes of

the data analysis, data cut-off for Part 2 will occur when 48 PFS events (progressions or deaths) have been observed.

Adverse events will be coded using the MedDRA and will be summarized by system organ class and preferred term. In addition, summaries of AEs by severity and relationship to study drug will be presented.

Further details are specified in the Statistical Analysis Plan.

13.4.2 Demographics and Other Subject Characteristics

The number of subjects enrolled in Part 1 and Part 2 will be summarized separately.

The number and percentage of subjects screened, randomly assigned to treatment, failed screening by the primary reasons for screening failure, treated, completed the trial, and discontinued by the primary reason for discontinuation will be displayed by treatment and overall.

Subjects who were randomly assigned to trial medication but who discontinued prior to treatment with trial medication will be presented. Subjects who are treated but who were not randomly assigned to trial medication will be presented. All treated subjects who discontinue prematurely from the study will be presented. Randomized subjects for whom the blind was broken will also be presented.

All baseline and demographic variables will be summarized descriptively, using mean, standard deviation, median, minimum, median, and maximum for continuous measures, and frequency count and percentage for categorical and binary measures. The results will be presented in summary tables and by-subject listings.

The comparability of the treatment groups for baseline and demographic characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed. Demographic variables will be summarized by treatment and overall by either descriptive statistics or categorical tables:

- Continuous demographic baseline variables: age (years), body weight, height
- Categorical demographic baseline variables: age, gender, race

Medical history will also be summarized.

13.4.3 Primary Outcome Measure

13.4.3.1 Primary Safety Outcome Measure

The primary safety outcome measure is the occurrence of DLTs (Part 1) (see Section 8.4.1).

Where appropriate, point estimates and 95% two-sided confidence intervals (CIs) will be calculated for all safety outcome measures by treatment group.

For the determination of the RP2D, the analysis of the occurrence of DLTs will be performed on a subset of the safety analysis set, including all evaluable subjects. Subjects will be considered evaluable once they either complete their first treatment cycle or withdraw from study during the first treatment cycle due to DLT. The percentage of subjects experiencing DLT during their first treatment cycle will be displayed along with corresponding 95% CIs, where appropriate. The RP2D will be defined as the highest dose level examined at which <33% of evaluable subjects experience a DLT during the first treatment cycle.

13.4.3.2 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is PFS (Part 2), defined as time between treatment initiation and tumor progression (per RECIST v1.1) or death from any cause (see Section 8.4.1).

Median PFS and corresponding 95% CI for each of the 2 treatment groups will be estimated based on the KM methodology for time-to-event data analysis. Other percentiles of PFS may also be provided if estimable. Percentages and 95% CI of subjects with PFS at Week 16 and other time points will also be based on the KM estimates. In addition, KM plots and a one-sided log-rank test will be presented.

In addition, median PFS of each stratum based on KRAS/NRAS status within will be reported and a KM curve will be displayed for each study arm.

13.4.4 Secondary Outcome Measures

13.4.4.1 Immunogenicity Outcome Measures

The measure of immunogenicity is based on (see Section 8.4.2.1):

- Occurrence of binding and/or neutralizing anti imalumab antibodies
- Incidence and severity of infusion reactions after imalumab

13.4.4.2 Safety Outcome Measures

The safety outcome measures are (see Section [8.4.2.2](#)):

- Occurrence of SAEs and/or TEAEs, regardless of causality or relationship to study drug using NCI CTCAE v4.03
- Other safety measurements: physical or instrumental examinations, ECGs, vital signs, clinically relevant changes in instrumental examinations or laboratory values

Adverse events will be regarded as treatment emergent (ie, TEAEs) if they started on or after the date and time of administration of the first dose of study drug, or if they were present prior to the administration of the first dose of study drug and increased in severity during the study.

The number of subjects who experience SAEs and TEAEs will be tabulated and summarized by treatment group. The total number of subjects and events and the corresponding rates will be presented.

In addition, tables will be prepared to list each AE, the number of subjects in each treatment group who experienced an AE at least once, and the rate of subjects with AE(s). Adverse events will be grouped by system organ class. Each event will then be divided into defined severity grades (as described in Section [12.1.2.1](#)). The tables will also divide the AEs into those considered related (a “possibly related” or a “probably related” AE will be considered as a “related AE”) to the treatment and those considered unrelated (an “unlikely related” or an “unrelated” AE will be considered as an “unrelated” AE).

All AEs for each subject, including the same event on several occasions, will be listed, detailing both the MedDRA preferred term and the original verbatim term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

Electrocardiograms and vital signs will be summarized using appropriate descriptive statistics. For each clinical laboratory value and change from baseline, summaries will be made via descriptive statistics (ie, mean, median, standard deviation, and range). A summary table showing incidence of clinically significant treatment-emergent laboratory values will be provided. Shift tables showing incidence of new or worsening clinically significant findings from baseline to endpoint will be provided.

13.4.4.3 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are (see Section [8.4.2.3](#)):

- Response evaluation according to RECIST v1.1
- OS time from randomization to death of any cause

The ORR and CBR and the exact 2-sided 95% CI will be reported for each treatment arm, and by KRAS status.

Overall survival will also be summarized similarly to PFS.

13.4.4.4 Secondary Pharmacokinetic Outcome Measure

The secondary PK outcome measure is the plasma concentrations of imalumab (see Section [8.4.2.4](#)):

Plasma concentrations of imalumab will be listed and summarized descriptively, as appropriate, for each treatment group.

Imalumab plasma PK will be characterized using a population PK modeling approach, in combination with PK data from other studies. Results of population PK modeling and PK/PD correlations will be reported in a separate report.

13.4.4.5 Secondary Quality of Life Outcome Measures

The secondary QoL outcome measure is using a validated general questionnaire (see Section [8.4.2.5](#)):

- The EORTC QLQ-C30 questionnaire

13.4.5 Exploratory Outcome Measures

The exploratory outcome measures are:

- Levels of oxMIF and total MIF in plasma

The levels of oxMIF and total MIF in plasma will be presented in summary tables. Changes in the levels following imalumab treatment from baseline will be computed, as applicable and appropriate.

- Tumor-associated genetic alterations in blood/urine (for subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide consent for exploratory biomarker analyses)

The sponsor will obtain available historical tumor mutational testing results for subjects.

Other exploratory measures are assessed using validated general questionnaires (see Section 8.4.3):

- EORTC QLQ-CR29
- EQ-5D

13.5 Planned Interim Analysis of the Study

An interim analysis will be implemented for planning purposes when 33 PFS events have been observed. The interim analysis will primarily include a summary of safety (as measured by incidence of TEAEs) and PFS by treatment arm. The DSMB will be included in review of the interim analysis data (see Section 15.4.2).

For the purposes of the final analysis, data cut-off for Part 2 will occur when 48 PFS events (progressions or deaths) have been observed.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol, as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

15.4.1 Data Safety Monitoring (Part 1)

A Data Review Committee (DRC) will review accumulating unblinded safety data of the subjects enrolled in Part 1.

The DRC members must include at least one participating investigator, the sponsor-designated Medical Monitor, and a sponsor representative (non-voting).

The DRC will meet for safety reviews after 3 subjects in a dosing cohort have completed the first treatment cycle (ie, after 28 days) to decide if additional subjects must be enrolled or if the next dose level can be opened. All available safety data will also be provided for subjects who discontinue prior to this time. At the end of the escalation phase, the DRC will determine the RP2D for each imalumab combination, or decide if an intermediate dose level will be explored.

Decisions will be made using the stopping rules and dose escalation procedures defined within the protocol (see Section 8.2.1.1) and shown in [Figure 1](#).

15.4.2 Data Safety Monitoring Board (Part 2)

This part of the study will be monitored by a DSMB. This DSMB will be composed of recognized experts in the field of oncology for clinical care and research, one of whom at least must be independent from the sponsor.

The DSMB will evaluate the safety data during Part 2 of the trial on a quarterly basis. The DSMB will also review data from the interim analysis (see Section 13.5). The DSMB can stop the trial for safety reasons at any time. Ad hoc reviews may be scheduled by the sponsor, as warranted, based on the number/severity of AEs/DLTs experienced by subjects in the ongoing trial. The composition, activities, and responsibilities of the DSMB are described in further detail in the DSMB Charter.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

During both phases of the study (Part 1 and Part 2), local laboratories will be used for hematology and clinical chemistry assessments. Inter-laboratory standardization methods for hematology and clinical chemistry assessments will be described in the data management plan.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of subjects into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose subjects for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. An assent form may be provided and should be signed by subjects less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, subjects or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which has been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

The sponsor will obtain available historical tumor mutational testing results for subjects. In subjects who provide consent, blood and urine samples will be collected for an optional exploratory analysis, to assess the effect of imalumab in combination with 5-FU/LV or panitumumab on tumor-associated genetic biomarkers.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAER Forms, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

Only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

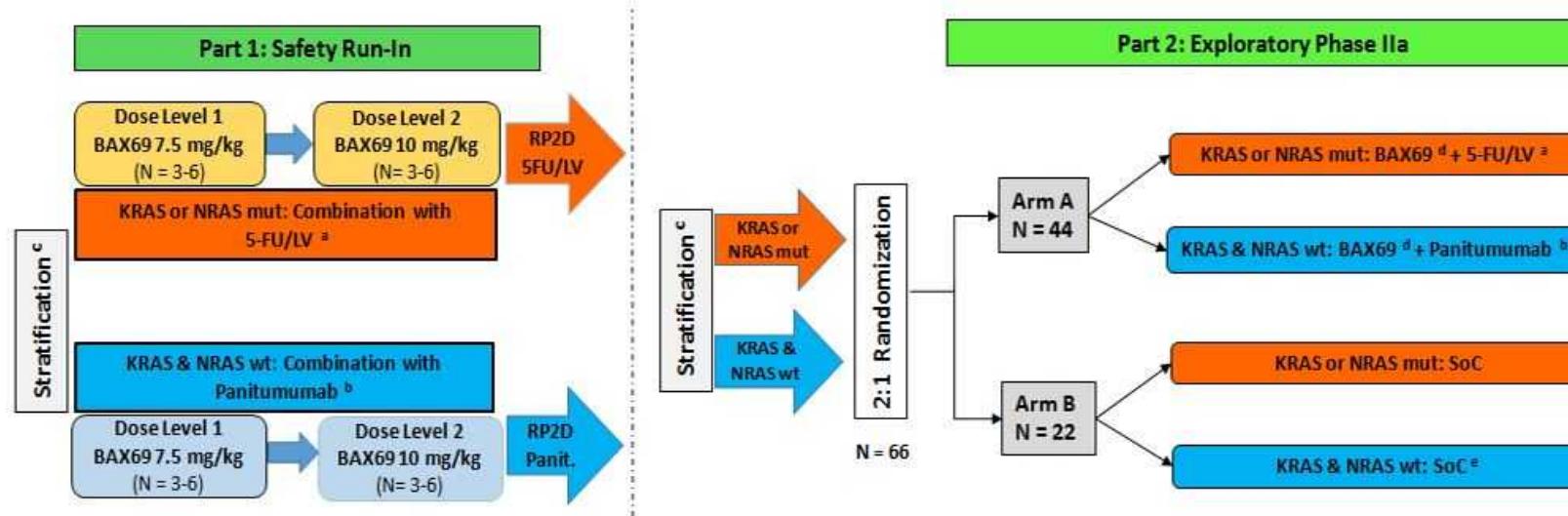
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study 391401 Schematic

Figure 2
Study 391401 Schematic



Abbreviations: 5-FU=5-fluorouracil; BAX69=imalumab; LV=leucovorin; mut=mutated; RP2D=recommended Phase 2 dose; SoC=standard of care; wt=wild type.

^a 5-FU/LV regimen: Leucovorin 400 mg/m² IV infusion over 2 hours followed by 5-FU 2400 mg/m² IV infusion over 46 hours Q2W.

^b Panitumumab dose = 6 mg/kg IV Q2W over 60 min.

^c Stratification is by KRAS/ NRAS status (mut or wt).

^d Imalumab dose for Part 2 will be the RP2D for QW dosing determined in Part 1 for each combination.

^e Dose according to drug label; choice includes panitumumab in KRAS and NRAS wt group only.

20.2 Schedule of Study Procedures and Assessments

Table 3
Schedule of Study Procedures and Assessments: Parts 1 and 2

Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b	
			Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28			
Study Days Procedures/Assessments	Days -28 to -1	Day 1 Predose							
Treatment Schedule									
Imalumab administration (QW) (Part 1; Part 2, Arm A)			Day 1	Day 8	Day 15	Day 22			
5-FU/LV or panitumumab administration (Q2W) (Part 1; Part 2, Arm A)			Day 1		Day 15				
Visit window (days)		± 2	± 2	± 2	± 2	± 2	± 2	± 7	
Informed consent ^c	X								
Eligibility criteria	X	X							
Demographics	X								
Relevant medical and surgical history	X								
Entry into IRT System	X	X ^d	Day 1 ^d	Day 8 ^d	Day 15 ^d	Day 22 ^d	X		
Vital signs ^e	X	X	Day 1	Day 8	Day 15	Day 22	X	X	
Physical examination	X	X	Day 1		Day 15		X	X	
ECOG PS	X	X	Day 1				X	X	

Table 3
Schedule of Study Procedures and Assessments: Parts 1 and 2

Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit^b
			Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Study Days	Days -28 to -1	Day 1 Predose						
Treatment Schedule								
EORTC QLQ-C30		X					X	X
EORTC QLQ-CR29		X					X	X
EQ-5D		X					X	X
12-lead ECG ^f	X	X	Day 1				X	X
ECHO/MUGA	X							
Hematology ^g	X	X	Day 1	Day 8	Day 15	Day 22	X	X
Chemistry/coagulation ^g	X	X	Day 1	Day 8 (Cycle 1 only)	Day 15		X	X
Pregnancy test ^h (if applicable)	X	X	Day 1				X	X
Urinalysis	X	X	Day 1				X	X
Genetic testing ⁱ (KRAS/NRAS)	X							
Tumor measurement (RECIST v1.1) ^j	X					Day 28 of Cycle 2 and then every other cycle	X ^k	X ^k

Table 3
Schedule of Study Procedures and Assessments: Parts 1 and 2

Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit^b
			Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Study Days	Days -28 to -1	Day 1 Predose						
Treatment Schedule								
Blood sampling for immunogenicity (ADA and NADA)	X						X	X
PK blood samples (imalumab plasma levels)	X	X	Day 1 and Day 2 OR Day 4 ^l	Day 8 ^l	Day 15 ^l	Day 22 ^l		
Blood samples for PD biomarkers (oxMIF and total MIF)	X	X	Day 1 and Day 2 OR Day 4 ^l	Day 8 ^l	Day 15 ^l	Day 22 ^l		
Blood sample for genetic biomarkers (cfDNA) ^m	X					Day 28 of Cycle 1 and then every other cycle	X	
Urine sample for genetic biomarkers (cfDNA) ^m	X					Day 28 of Cycle 1 and then every other cycle	X	

Table 3 Schedule of Study Procedures and Assessments: Parts 1 and 2								
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Treatment Schedule								
Adverse events ⁿ	X	X	X	X	X	X	X	X
Concomitant medications/non-drug therapies	X	X	X	X	X	X	X	X

Abbreviations: 5-FU=5-fluorouracil; ADA=anti-drug antibody; AE=adverse event; C1D1=Cycle 1 Day 1; cfDNA=cell-free DNA; CT=computerized tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CR29=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for colorectal cancer 29; EQ-5D=European Quality of Life – 5 Dimensions; IRT=Interactive Response Technology; KRAS=Kirsten rat sarcoma viral oncogene homolog; LV=leucovorin; MIF=macrophage migration inhibitory factor; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; NADA=neutralizing anti-drug antibody; NRAS=neuroblastoma RAS viral (v-ras) oncogene homolog; oxMIF=oxidated macrophage migration inhibitory factor; PD=pharmacodynamic; PK=pharmacokinetic; Q2W=every 2 weeks; QW=every week; RECIST=Response Evaluation Criteria in Solid Tumors; SoC=standard of care.

^a Treatment cycles are defined in this study as 4-week cycles. In each treatment cycle, imalumab is administered QW, and 5-FU/LV and panitumumab are administered Q2W in 4-week cycles. Treatment cycles will continue until progression, unacceptable toxicities, or withdrawal of consent.

^b The Safety Follow-up Visit should occur 30 (± 7) days after the last dose of study treatment. For subjects who have stopped study drug or have documented disease progression, post-study telephone calls to assess overall survival will be made by site staff every 3 months.

^c Subject informed consent occurs at screening, prior to any study-specific procedure.

^d IRT will be utilized at screening and baseline visits for all subjects (Part 1 and Part 2), at all subsequent study visits in Part 1, and all subsequent study visits in Part 2 for subjects in Arm A only.

^e Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate, are to be measured after a 5-minute rest. Sitting position is recommended for blood pressure measurement. Height and body weight will also be recorded. On the day of imalumab administration, vital signs will be taken within 30 minutes prior to dosing and within 30 minutes after completion of imalumab infusion. Weekly monitoring to be done in Cycle 1 only, then Q2W.

Continued on next page

Continued

- ^f The 12-lead ECG assessment at Screening should be performed no earlier than 1 week before C1D1. The 12-lead ECG assessment should be performed predose and 2 (\pm 1) hours postdose on Day 1 (Baseline, C1D1).
- ^g Laboratory assessments should be evaluated before drug administration. Immediately prior to Cycle 1, laboratory assessments can be performed either on Day -1 or on Day 1 predose. Hematology tests will be done weekly during each treatment cycle. Chemistry/coagulation tests will be done on Day 1 and Day 15 of each treatment cycle, and Day 8 of Cycle 1 only. Laboratory tests include hematology (complete blood count with differential and platelet counts) and biochemistry (creatinine, creatinine clearance according to Cockcroft-Gault, sodium, potassium, calcium, magnesium, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, C-reactive protein, and blood urea nitrogen). Coagulation panel includes International Normalized Ratio and activated partial thromboplastin time.
- ^h Serum human chorionic gonadotropin to be tested at screening; urine dipstick test to be performed on Day 1 of each cycle (prior to dosing), End of Study/Early Termination Visit, and at Safety Follow-up. A serum pregnancy test will be performed to confirm if a positive result is obtained in a dipstick test.
- ⁱ If not readily available, genetic testing for KRAS/NRAS mutation status needs to be done early enough to allow randomization within 4 weeks. If KRAS mutation status is known, the subject can start treatment while NRAS testing is pending.
- ^j Baseline CT or MRI scans can be accepted within 28 days prior to first imalumab administration (C1D1); assessments are to be repeated every 2 cycles using the same method at each measurement and tumor response evaluated before starting the next cycle. A 7-day window is permitted for all imaging studies for tumor measurement purposes.
- ^k A tumor measurement should be obtained at the End of Study/Early Termination visit, if no disease progression was confirmed previously and this visit occurs $>$ 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit. A tumor measurement should be obtained at the Safety Follow-up visit, if no disease progression was confirmed previously and this visit occurs $>$ 4 weeks after the last scan.
- ^l For subjects receiving imalumab treatment, blood samples for PK (imalumab plasma levels) and PD biomarkers (oxMIF and total MIF) will be collected at the times indicated in **Table 6. Cycle 1 only:** Blood samples will be collected predose and postdose on Day 1, on either Day 2 (24 \pm 4 h post first dose) OR Day 4 (72 \pm 8 h post first dose), and then predose and postdose on Day 8, Day 15, and Day 22.
- Subsequent treatment cycles:*** Blood samples will be collected predose and postdose only on Day 1.
- ^m Optional exploratory analysis for subjects treated with imalumab in combination with 5-FU/LV or panitumumab.
- ⁿ AEs to be collected on a continuous basis until the Safety Follow-up Visit.

In subjects randomized to SoC (Part 2, Arm B), all Screening assessments and procedures should be performed according to [Table 4](#) and Section 10.3.1. All Baseline assessments and procedures should be performed at C1D1 predose according to [Table 4](#) and Section 10.3.2. These assessments should be completed prior to drug administration. If the study subject is receiving SoC on a 4-week treatment cycle, the schedule of assessments should be as follows:

Table 4 Schedule of Study Procedures and Assessments: SoC Following Randomization (4-Week Cycles or if Subject is on Best Supportive Care)								
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Treatment Schedule								
SoC (Part 2, Arm B)			Dose according to Product Label					
Visit window (days)		±2	±2	±2	±2	±2	±2	±7
Informed consent ^c	X							
Eligibility criteria	X	X						
Demographics	X							
Relevant medical and surgical history	X							
Entry into IRT System	X	X ^d					X	
Vital signs ^e	X	X	Day 1	Day 8	Day 15	Day 22	X	X
Physical examination	X	X	Day 1		Day 15		X	X
ECOG PS	X	X	Day 1				X	X

Table 4 Schedule of Study Procedures and Assessments: SoC Following Randomization (4-Week Cycles or if Subject is on Best Supportive Care)								
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Treatment Schedule								
EORTC QLQ-C30		X					X	X
EORTC QLQ-CR29		X					X	X
EQ-5D		X					X	X
12-lead ECG ^f	X	X	Day 1				X	X
ECHO/MUGA	X							
Hematology ^g	X	X	Day 1	Day 8	Day 15	Day 22	X	X
Chemistry/coagulation ^g	X	X	Day 1	Day 8 (Cycle 1 only)	Day 15		X	X
Pregnancy test ^h (if applicable)	X	X	Day 1				X	X
Urinalysis	X	X	Day 1				X	X
Genetic testing ⁱ (KRAS/NRAS)	X							
Tumor measurement (RECIST v1.1) ^j	X					Day 28 of Cycle 2 and then every other cycle	X ^k	X ^k
Adverse Event ^l	X	X	X	X	X	X	X	X

Table 4 Schedule of Study Procedures and Assessments: SoC Following Randomization (4-Week Cycles or if Subject is on Best Supportive Care)									
Trial Periods		Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle^a				End of Study/ Early Termination Visit	Safety Follow-Up Visit^b
Study Days	Procedures/Assessments	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21	Days 22 to 28		
Treatment Schedule									
Concomitant medications/non-drug therapies		X	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; C1D1=Cycle 1 Day 1; cfDNA=cell-free DNA; CT=computerized tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CR29=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for colorectal cancer 29; EQ-5D=European Quality of Life – 5 Dimensions; IRT=Interactive Response Technology; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SoC=standard of care.

^a Treatment cycles for SoC are defined in this study as 3-week or 4-week cycles. Treatment cycles will continue until progression, unacceptable toxicities, or withdrawal of consent.

^b The Safety Follow-up Visit should occur 30 (± 7) days after the last dose of study treatment. For subjects who have stopped study drug or have documented disease progression, post-study telephone calls to assess overall survival will be made by site staff every 3 months.

^c Subject informed consent occurs at screening, prior to any study-specific procedure.

^d IRT will be utilized at screening and baseline visits only for all subjects randomized to Arm B (Part 2) to receive SoC/best supportive care.

^e Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate, are to be measured after a 5-minute rest. Sitting position is recommended for blood pressure measurement. Height and body weight will also be recorded. Weekly monitoring to be done in Cycle 1 only, then Q2W. Vital signs should be evaluated both predose and postdose during treatment with SoC.

^f The 12-lead ECG assessment should be performed predose and 2 (± 1) hours postdose on Day 1 (Baseline, C1D1).

Continued on Next Page

Continued

- ^g Laboratory assessments should be evaluated before drug administration. Immediately prior to Cycle 1, laboratory assessments can be performed either on Day -1 or on Day 1 predose. Hematology tests will be done weekly during each treatment cycle. Chemistry/coagulation tests will be done on Day 1 and Day 15 of each treatment cycle, and Day 8 of Cycle 1 only. Laboratory tests include hematology (complete blood count with differential and platelet counts) and biochemistry (creatinine, creatinine clearance according to Cockcroft-Gault, sodium, potassium, calcium, magnesium, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, C-reactive protein, and blood urea nitrogen). Coagulation panel includes International Normalized Ratio and activated partial thromboplastin time.
- ^h Urine dipstick test to be performed on Day 1 of each cycle (prior to dosing), End of Study/Early Termination Visit, and at Safety Follow-up. A serum pregnancy test will be performed to confirm if a positive result is obtained in a dipstick test.
- ⁱ If not readily available, genetic testing for KRAS/NRAS mutation status needs to be done early enough to allow randomization within 4 weeks. If KRAS mutation status is known, the subject can start treatment while NRAS testing is pending.
- ^j Baseline CT or MRI scans can be accepted within 28 days prior to first imalumab administration (C1D1); assessments are to be repeated every 2 cycles using the same method at each measurement and tumor response evaluated before starting the next cycle. A 7-day window is permitted for all imaging studies for tumor measurement purposes.
- ^k A tumor measurement should be obtained at the End of Study/Early Termination visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit. A tumor measurement should be obtained at the Safety Follow-up visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan.
- ^l AEs to be collected on a continuous basis until the Safety Follow-up Visit.

In subjects randomized to SoC (Part 2, Arm B), all Screening assessments and procedures should be performed according to [Table 5](#) and Section 10.3.1. All Baseline assessments and procedures should be performed at C1D1 predose according to [Table 5](#) and Section 10.3.2. These assessments should be completed prior to drug administration. If the study subject is receiving SoC on a 3-week treatment cycle, the schedule of assessments should be as follows:

Table 5 Schedule of Study Procedures and Assessments: SoC Following Randomization (3-Week Cycles)							
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a			End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21		
Treatment Schedule							
SoC (Part 2, Arm B)			Dose According to Product Label				
Visit window (days)		±2	±2	±2	±2	±2	±7
Informed consent ^c	X						
Eligibility criteria	X	X					
Demographics	X						
Relevant medical and surgical history	X						
Entry into IRT System	X	X ^d				X	
Vital signs ^e	X	X	Day 1	Day 8	Day 15	X	X
Physical examination	X	X	Day 1		Day 15	X	X
ECOG PS	X	X	Day 1			X	X

Table 5 Schedule of Study Procedures and Assessments: SoC Following Randomization (3-Week Cycles)							
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a			End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21		
Treatment Schedule							
EORTC QLQ-C30		X				X	X
EORTC QLQ-CR29		X				X	X
EQ-5D		X				X	X
12-lead ECG ^f	X	X	Day 1			X	X
ECHO/MUGA	X						
Hematology ^g	X	X	Day 1	Day 8	Day 15	X	X
Chemistry/coagulation ^g	X	X	Day 1	Day 8 (Cycle 1 only)	Day 15	X	X
Pregnancy test ^h (if applicable)	X	X	Day 1			X	X
Urinalysis	X	X	Day 1			X	X
Genetic testing ⁱ (KRAS/NRAS)	X						
Tumor measurement (RECIST v1.1) ^j	X				Every 8 weeks	X ^k	X ^k

Table 5 Schedule of Study Procedures and Assessments: SoC Following Randomization (3-Week Cycles)							
Trial Periods	Screening Visit	Baseline Visit	Study Visits Per Treatment Cycle ^a			End of Study/ Early Termination Visit	Safety Follow-Up Visit ^b
Study Days	Days -28 to -1	Day 1 Predose	Days 1 to 7	Days 8 to 14	Days 15 to 21		
Treatment Schedule							
Adverse Event ^c	X	X	X	X	X	X	X
Concomitant medications/non-drug therapies	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; C1D1=Cycle 1 Day 1; cfDNA=cell-free DNA; CT=computerized tomography; ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CR29=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for colorectal cancer 29; EQ-5D=European Quality of Life – 5 Dimensions; IRT=Interactive Response Technology; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SoC=standard of care.

^a Treatment cycles for SoC are defined in this study as 3-week or 4-week cycles. Treatment cycles will continue until progression, unacceptable toxicities, or withdrawal of consent.

^b The Safety Follow-up Visit should occur 30 (\pm 7) days after the last dose of study treatment. For subjects who have stopped study drug or have documented disease progression, post-study telephone calls to assess overall survival will be made by site staff every 3 months.

^c Subject informed consent occurs at screening, prior to any study-specific procedure.

^d IRT will be utilized at screening and baseline visits only for all subjects randomized to Arm B (Part 2) to receive SoC/best supportive care.

^e Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate, are to be measured after a 5-minute rest. Sitting position is recommended for blood pressure measurement. Height and body weight will also be recorded. Weekly monitoring to be done in Cycle 1 only, then Q2W. Vital signs should be evaluated both predose and postdose during treatment with SoC.

^f The 12-lead ECG assessment should be performed predose and 2 (\pm 1) hours postdose on Day 1 (Baseline, C1D1).

Continued on next Page

Continued

- ^g Laboratory assessments should be evaluated before drug administration. Immediately prior to Cycle 1, laboratory assessments can be performed either on Day -1 or on Day 1 predose. Hematology tests will be done weekly during each treatment cycle. Chemistry/coagulation tests will be done on Day 1 and Day 15 of each treatment cycle, and Day 8 of Cycle 1 only. Laboratory tests include hematology (complete blood count with differential and platelet counts) and biochemistry (creatinine, creatinine clearance according to Cockcroft-Gault, sodium, potassium, calcium, magnesium, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, C-reactive protein, and blood urea nitrogen). Coagulation panel includes International Normalized Ratio and activated partial thromboplastin time.
- ^h Urine dipstick test to be performed on Day 1 of each cycle (prior to dosing), End of Study/Early Termination Visit, and at Safety Follow-up. A serum pregnancy test will be performed to confirm if a positive result is obtained in a dipstick test.
- ⁱ If not readily available, genetic testing for KRAS/NRAS mutation status needs to be done early enough to allow randomization within 4 weeks. If KRAS mutation status is known, the subject can start treatment while NRAS testing is pending.
- ^j Baseline CT or MRI scans can be accepted within 28 days prior to first imalumab administration (C1D1); assessments are to be repeated **every 8 weeks** using the same method at each measurement and tumor response evaluated before starting the next cycle. A 7-day window is permitted for all imaging studies for tumor measurement purposes.
- ^k A tumor measurement should be obtained at the End of Study/Early Termination visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit. A tumor measurement should be obtained at the Safety Follow-up visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan.
- ^l AEs to be collected on a continuous basis until the Safety Follow-up Visit.

Table 6
Schedule of Pharmacokinetic and Pharmacodynamic Sample Collections (Parts 1 and 2) for Subjects Receiving Imalumab Treatment

Measurement of Imalumab, oxMIF, and Total MIF	Screening Visit	Cycle 1				Subsequent Cycles
		Dose 1 (Day 1)	Dose 2 (Day 8)	Dose 3 (Day 15)	Dose 4 (Day 22)	
Time Interval^a for Collection of Blood Sample	Days -28 to -1					
No infusion (Screening)	1 sample					
-2 to 0 hours before infusion start		1 sample ^b	1 sample	1 sample	1 sample	1 sample
0 to 2 hours after infusion		1 sample	1 sample	1 sample	1 sample	1 sample
6 to 8 hours after infusion		1 sample				
24 ± 4 hours OR 72 ± 8 hours after infusion		1 sample				

Abbreviations: MIF=macrophage migration inhibitory factor; oxMIF=oxidated macrophage migration inhibitory factor.

^a The scheduled samples may be collected at any time within the time interval specified.

^b This sample may be collected at any time on Day 1 before infusion start.

Table 7
Blood Volumes (Parts 1 and 2) for Lab Tests and PK/PD for Subjects Receiving Imalumab Treatment

Assessments	Screening Visit	Cycle 1				Safety and PK/PD Cycle 1	Each Subsequent Cycle
	Days -28 to -1	Dose 1 (Day 1)	Dose 2 (Day 8)	Dose 3 (Day 15)	Dose 4 (Day 22)	Total	Total
Hematology/blood chemistry/coagulation ^a	3 mL	10 mL	3mL	3 mL	3 mL	19 mL	Day 1, Day 8, Day 15 and Day 22 12 mL
Imalumab concentrations, oxMIF, and total MIF	8 mL	32 mL ^b	16 mL	16 mL	16 mL	80 mL	Day 1 (predose and postdose) 16 mL
Total	11 mL	42 mL	19 mL	19 mL	19 mL	99 mL	28 mL

Abbreviations: MIF=macrophage migration inhibitory factor; oxMIF=oxidized macrophage migration inhibitory factor; PD=pharmacodynamic; PK=pharmacokinetic; RBC=red blood cells; WBC=white blood cells.

^a Laboratory tests include hematology (red blood cells, white blood cells, neutrophils, platelets, hematocrit, and hemoglobin) and biochemistry (creatinine, creatinine clearance according to Cockcroft-Gault, sodium, potassium, calcium, magnesium, glucose, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, C-reactive protein, blood urea, International Normalized Ratio, and activated partial thromboplastin time).

Table 8
Blood and Urine Volumes (Parts 1 and 2) for Optional Genetic Biomarkers cfDNA Analysis for Subjects Receiving Imalumab Treatment

Assessments	Screening Days -28 to -1	Cycle 1 Day 28	Every Other Cycle Day 28 ^a	End of Study/ Early Termination Visit
Blood sample for genetic biomarkers (cfDNA)	10 mL	10 mL	10 mL	10 mL
Urine sample for genetic biomarkers (cfDNA)	30 mL	30 mL	30 mL	30 mL
Total	40 mL	40 mL	40 mL	40 mL

Abbreviations: 5-FU=5-fluorouracil; cfDNA=cell-free DNA; LV=leucovorin.

^a For example, Cycle 3 Day 28, Cycle 5 Day 28, Cycle 7 Day 28, etc., in subjects receiving imalumab + 5-FU/LV or imalumab + panitumumab (Arm A).

21. REFERENCES

1. Morand EF. New therapeutic target in inflammatory disease: macrophage migration inhibitory factor. *Intern.Med.J.* 2005;35: 419-426.
2. Larson DF, Horak K. Macrophage migration inhibitory factor: controller of systemic inflammation. *Crit.Care* 2006;10: 138.
3. Lan HY. Role of macrophage migration inhibition factor in kidney disease. *Nephron.Exp.Nephrol.* 2008;109: e79-e83.
4. Mitchell RA, Metz CN, Peng T et al. Sustained mitogen-activated protein kinase (MAPK) and cytoplasmic phospholipase A2 activation by macrophage migration inhibitory factor (MIF). Regulatory role in cell proliferation and glucocorticoid action. *J.Biol.Chem.* 1999;274: 18100-18106.
5. Renner P, Roger T, Calandra T. Macrophage migration inhibitory factor: gene polymorphisms and susceptibility to inflammatory diseases. *Clin.Infect.Dis.* 2005;41 Suppl 7: S513-S519.
6. Flaster H, Bernhagen J, Calandra T et al. The macrophage migration inhibitory factor-glucocorticoid dyad: regulation of inflammation and immunity. *Mol.Endocrinol.* 2007;21: 1267-1280.
7. Javeed A, Zhao Y, Zhao Y. Macrophage-migration inhibitory factor: role in inflammatory diseases and graft rejection. *Inflamm.Res.* 2008;57: 45-50.
8. Greven D, Leng L, Bucala R. Autoimmune diseases: MIF as a therapeutic target. *Expert Opin.Ther.Targets* 2010;14: 253-264.
9. Bucala R, Donnelly SC. Macrophage migration inhibitory factor: a probable link between inflammation and cancer. *Immunity.* 2007;26: 281-285.
10. Meyer-Siegler KL, Iczkowski KA, Vera PL. Further evidence for increased macrophage migration inhibitory factor expression in prostate cancer. *BMC Cancer.* 2005;5: 73.
11. Winner M, Leng L, Zundel W et al. Macrophage migration inhibitory factor manipulation and evaluation in tumoral hypoxic adaptation. *Methods Enzymol.* 2007;435: 355-369.

12. Hagemann T, Robinson SC, Thompson RG et al. Ovarian cancer cell-derived migration inhibitory factor enhances tumor growth, progression, and angiogenesis. *Mol.Cancer Ther.* 2007;6: 1993-2002.
13. Chesney J, Metz C, Bacher M et al. An essential role for macrophage migration inhibitory factor (MIF) in angiogenesis and the growth of a murine lymphoma. *Mol.Med.* 1999;5: 181-191.
14. Meyer-Siegler KL, Iczkowski KA, Vera PL. Macrophage migration inhibitory factor is increased in the urine of patients with urinary tract infection: macrophage migration inhibitory factor-protein complexes in human urine. *J.Urol.* 2006;175: 1523-1528.
15. Nishihira J, Ishibashi T, Fukushima T et al. Macrophage migration inhibitory factor (MIF): Its potential role in tumor growth and tumor-associated angiogenesis. *Ann.N.Y.Acad.Sci.* 2003;995: 171-182.
16. Noels H, Bernhagen J, Weber C. Macrophage migration inhibitory factor: a noncanonical chemokine important in atherosclerosis. *Trends Cardiovasc.Med.* 2009;19: 76-86.
17. Rendon BE, Willer SS, Zundel W et al. Mechanisms of macrophage migration inhibitory factor (MIF)-dependent tumor microenvironmental adaptation. *Exp.Mol.Pathol.* 2009;86: 180-185.
18. Verjans E, Noetzel E, Bektas N et al. Dual role of macrophage migration inhibitory factor (MIF) in human breast cancer. *BMC Cancer.* 2009;9: 230.
19. He XX, Chen K, Yang J et al. Macrophage migration inhibitory factor promotes colorectal cancer. *Mol.Med.* 2009;15: 1-10.
20. Choi S, Kim HR, Leng L et al. Role of macrophage migration inhibitory factor in the regulatory T cell response of tumor-bearing mice. *J.Immunol.* 2012;189: 3905-3913.
21. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur.J.Cancer* 2009;45:228-247.
22. Misale S, Yaeger R, Hobor S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature* 2012;486:532-536.
23. Thierry AR, Mouliere F, El Messaoudi S, et al. Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. *Nat Med.* 2014;20:430-5.

24. Haber DA, Velculescu VE. Blood-based analyses of cancer: circulating tumor cells and circulating tumor DNA. *Cancer Discov.* 2014;4:650-661.
25. Tóth K, Barták BK, Tulassay Z, et al. Circulating cell-free nucleic acids as biomarkers in colorectal cancer screening and diagnosis. *Expert Rev Mol Diagn.* 2016;16:239-252.
26. Patel GS, Karapetis CS. Personalized treatment for advanced colorectal cancer: KRAS and beyond. *Cancer Manag Res.* 2013;5:387-400.
27. Spindler KL, Pallisgaard N, Vogelius I, et al. Quantitative cell-free DNA, KRAS, and BRAF mutations in plasma from patients with metastatic colorectal cancer during treatment with cetuximab and irinotecan. *Clin Cancer Res.* 2012;18:1177-1185.
28. Kapur P. Predictive biomarkers for response to therapy in advanced colorectal/rectal adenocarcinoma. *Critical Rev Oncog.* 2012;17:361-372.
29. Ashraf N, Kothari N, Kim R. Predictive biomarkers for anti-epidermal growth factor receptor therapy: beyond KRAS testing. *J Natl Compr Canc Netw* 2014; 12: 1433-42.
30. Peeters M, Olinas KM, Parker A et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res* 2013;19:1902–1912.
31. Patterson SD, Peeters M, Siena S et al. Comprehensive analysis of KRAS and NRAS mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408) [abstract]. *J Clin Oncol* 2013; 31(Suppl 1):Abstract 3617.
32. Sastre J, Massuti B, Pulido G et al. First-line single-agent panitumumab in frail elderly patients with wild-type KRAS metastatic colorectal cancer and poor prognostic factors: A phase II study of the Spanish Cooperative Group for the Treatment of Digestive Tumours. *Eur J Cancer.* 2015;51:1371-80.
33. Price TJ, Peeters M, Kim TW et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol.* 2014;15:569-79.

34. Amgen, Inc. Vectibix® (Panitumumab). Highlights of Prescribing Information.

Revised: 2015 MAR. Accessed 2015 OCT 01. Link to publisher's site:

http://pi.amgen.com/united_states/vectibix/vectibix_pi.pdf.

22. SUMMARY OF CHANGES

Protocol 391401: Amendment 5 (Global): 2016 MAY 09

Replaces: Amendment 2: 2015 JUL 13

In this section, changes described in the country-specific versions of the protocol, (dated 2015 DEC 16 [Germany version] and 2015 OCT 02 [UK version]) as well as further minor updates, are described and their rationale is given.

1. Throughout the document

Description of Change: “BAX69” was changed to “imalumab”, where appropriate. “Patients” was changed to “subjects” where appropriate, per the Baxalta style guide, except where patients not enrolled in a clinical study are described. Minor grammatical and/or administrative changes have been made, including ensuring abbreviations are defined on first use and used thereafter (where appropriate).

Purpose of Change: Administrative, and to improve the readability and/or clarity of the protocol.

2. Throughout the document

Description of Change: Changes made according to the updated Baxalta protocol template dated 2016 MAR 16.

Purpose of Change: To maintain consistency with current Baxalta protocol template.

3. Synopsis, Exploratory Objectives; Synopsis, Exploratory Outcome Measures (Genetic biomarkers); Synopsis, Study Design (Assessments); Section 7.4, Exploratory Objectives; Section 8.2.2 Part 2: Exploratory Phase 2a; Section 8.4.3 Exploratory Outcomes Measure; Section 10.3.1, Screening Assessments; Section 10.3.3.6 Day 28 (Cycle 1 and Every Other Cycle); Section 10.3.3.8 End of Study/Early Termination Visit; Section 13.4.5 Exploratory Outcome Measures; Section 16.3 Informed Consent

Description of Change: Exploratory objectives were added to this clinical study protocol, to be consistent with the exploratory outcome measures that will be made during the course of the study. A new exploratory outcome measure was added to this clinical study protocol (genetic biomarker analyses). These analyses will allow the characterization of tumor-associated genetic alterations in cfDNA samples from blood/urine that will be collected from subjects treated with imalumab in combination with 5-FU/LV or panitumumab who provide the additional consent for these biomarker analyses. The sponsor will also obtain available historical tumor mutational testing results for subjects.

Purpose of Change: Administrative (consistency of presenting exploratory objectives associated with all relevant exploratory outcome measures). The new genetic biomarker analyses were added to increase the knowledge of the effect of imalumab on well-known biomarkers of mCRC, as these biomarkers may correlate with clinical outcome (safety and efficacy).

4. Synopsis, Planned Duration of Subject Participation; Section 8.3, Duration of Study Period(s) and Subject Participation; Section 20.2, Schedule of Study Procedures and Assessments: Parts 1 and 2 (Table 3)

Description of Change: The duration of Screening was extended from 3 weeks (21 days) to 4 weeks (28 days).

Purpose of Change: The Screening period was extended in response to feedback from investigators.

5. Synopsis, Inclusion Criteria; Synopsis, Exclusion Criteria; Section 9.1, Inclusion Criteria; Section 9.2, Exclusion Criteria

Description of Change: Minor updates to inclusion criteria #8, #11, #13, and #15, as well as to exclusion criteria #3, #9, and #15, to match exactly the equivalent eligibility criteria presented in Sections 9.1 and 9.2. Inclusion criterion #12 was updated due to change in abbreviation use. Changed as follows:

- Inclusion criterion #8: “Known KRAS, NRAS mutation status (if unknown status for either of these genes, and no archival tissue is available, a fresh tumor biopsy will be ~~obtained~~^{made})”
- In inclusion criteria #11 and #13, the sub-bullets were changed from lower case roman numerals to lower case letters
- Inclusion criterion #11c: “Absolute neutrophil count (**ANC**) \geq 1,000/ μ L”
- Inclusion criterion #12: “Adequate renal function, defined as serum creatinine \leq 2.0 times ULN and creatinine clearance $>$ 50 mL/min or ~~eGFR~~ estimated **glomerular filtration rate** $>$ 50 ml/min/1.73 m²”
- Inclusion criterion #15: “~~Secondary~~ **contraception method contraceptive measures** could be either birth control pills, ~~or~~-patches, or intrauterine devices”
- Exclusion criterion #3: “Prior treatment with panitumumab for subjects with KRAS **wt and** ~~ANRAS~~ wt tumors”
- Exclusion criterion #9: “Left ventricular ejection fraction (LVEF) $<$ 40% as determined by echocardiogram (**ECHO**)/~~multigated acquisition scan~~ (**MUGA**) performed at screening or within 90 days prior to C1D1”
- Exclusion criterion #15: “Known history of, or active hepatitis B virus (HBV) **and/or**, hepatitis C virus (HCV), or active tuberculosis”

Purpose of Change: Administrative, correction for protocol inconsistencies.

6. Synopsis, Inclusion Criteria; Section 9.1, Inclusion Criteria

Description of Change: Inclusion criterion #3 was updated to clarify the definition of prior SoC treatment lines as “prior **cancer drug therapy** treatment lines **including SoC in the metastatic setting**.”

Purpose of Change: Administrative, to improve the clarity of the protocol.

7. Synopsis, Inclusion Criteria; Section 9.1, Inclusion Criteria

Description of Change: Updated inclusion criteria #15 and #16 to harmonize the contraceptive advice given in this clinical trial protocol with the SmPC for 5-FU. Added the following text:

- “In addition, these birth control methods must be continued for at least 180 days after last administration of 5-FU in subjects who receive this treatment.”

Purpose of Change: Safety, in response to feedback from the Medicines & Healthcare products Regulatory Agency (MHRA) (UK).

8. Synopsis, Exclusion Criteria; Section 9.2, Exclusion Criteria

Description of Change: Addition of a new exclusion criterion (#4) to exclude patients with KRAS wt and NRAS wt tumors who have a known history of keratitis, ulcerative keratitis, or severe dry eye, consistent with the SmPC for panitumumab.

The subsequent exclusion criteria were renumbered. Added the following text:

- “Known history of keratitis, ulcerative keratitis or severe dry eye in subjects with KRAS wt and NRAS wt tumors.”

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

9. Synopsis, Exclusion Criteria; Section 9.2, Exclusion Criteria

Description of Change: Updated exclusion criterion #5 to clarify that residual AEs from previous treatment > Grade 1 in severity of neuropathy and alopecia are not exclusionary for participation in this study.

Purpose of Change: Administrative, to improve the clarity of the protocol.

10. Synopsis, Exclusion Criteria; Section 9.2, Exclusion Criteria

Description of Change: Updated the wording of exclusion criterion #20 to replace “nursing” with “breastfeeding”.

Purpose of Change: Administrative, to improve the clarity of the protocol.

11. Synopsis, Sample Size Calculations; Section 13.1, Sample Size and Power Calculations; Section 20.1, Study 391401 Schematic (Figure 2)

Description of Change: Updated the wording to clarify the number of subjects in the Phase 2a (Part 2) of the study, while also harmonizing the wording in the Synopsis and Section 13.1: “With an enrollment ratio of 2:1, and taking into account the time for accrual of 1 year and an additional follow-up period of 6 months after the last subject is enrolled, the sample size needed is **a total of 44 approximately 22** subjects in ~~each~~ of the imalumab-containing treatment arms (~~imalumab + panitumumab and imalumab + 5-FU/LV~~) and **22 subjects** in the control arm (SoC), **for a total of 66 subjects**. The number of subjects allocated to each treatment in Part 2 of the study was removed from Figure 2 (Section 20.1).

Purpose of Change: Administrative correction.

12. Synopsis, Planned Statistical Analysis; Section 13.5, Planned Interim Analysis of the Study

Description of Change: The timing of the interim analysis was updated as follows: “An interim analysis will be implemented for planning purposes when 33 PFS events have been observed ~~in Part 2~~.”

Purpose of Change: Administrative, for clarification purposes.

13. Section 5, List of Abbreviations

Description of Change: Added new abbreviations (AUC_{0-tau}, C2D15, cfDNA, CTA, EGFR, MHRA, NGS, PEI, qPCR, RSI, SmPC, SUSAR and UK). Deleted abbreviations no longer used (HLT, MSI and SMQ). Ensured that the list of abbreviations is in alphabetical order. Added “Continued” at the top of each page of the List of Abbreviations per Baxalta style guide.

Purpose of Change: Administrative.

14. Section 6.1.4, Genetic Biomarkers Analysis; Section 21, References

Description of Change: A new section was added to provide background information describing findings from previous studies of mCRC and the effect of changes in KRAS/NRAS mutation status during treatment (acquired treatment resistance). This new section provides the rationale for the addition of the genetic biomarkers analysis to this clinical study. Relevant publications were added to the References section to support the additional information summarized in this section.

Purpose of Change: Administrative, to provide context for the new genetic biomarkers analysis that was added to this clinical study protocol.

15. Section 6.1.5.1, Dose Rationale

Description of Change: Updated the data cut-off date for the safety data that contributed to the dose rationale for this study.

- “30 Sep 2014” changed to “2015 JUL 01”.

Purpose of Change: Administrative, in response to feedback from the MHRA (UK) and Paul-Ehrlich-Institute (PEI, Germany).

16. Section 6.1.5.4, Rationale for Selection of Combination Therapies, Panitumumab

Description of Change: Included rationale for the inclusion of subjects in this study with ECOG PS 0-2 and potential treatment with panitumumab. Added the following text:

- “Panitumumab has been approved in several countries including the United States (US) and Germany as standard therapy. The sponsor feels it is justified to administer panitumumab to subjects in this study with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2. Panitumumab has been shown to be well tolerated in frail elderly patients (ECOG \leq 3) with KRAS wt mCRC and poor prognostic factors in a Phase 2 study of the Spanish Cooperative Group for the Treatment of Digestive Tumours.³² In addition, panitumumab and cetuximab were compared in a randomized Phase 3 study in patients with chemotherapy-refractory KRAS wt mCRC (ECOG \leq 2).³³ The incidence of adverse events (AEs) of any grade and grade 3-4 AEs was similar across treatment groups.”
- As this is now the first use of the terms “United States”, “Eastern Cooperative Oncology Group”, “Performance Status” and “adverse events” within the body of the protocol, subsequent use of these terms has been changed to “US” (Section 8.1), “ECOG” and “PS” (Section 6.3), “AEs” (applied as necessary throughout).

Purpose of Change: Safety, in response to feedback from the MHRA (UK); Administrative (first use of terms and abbreviations).

17. Section 6.3, Population to be Studied; Section 8.1 Study Design

Description of Change: The definition of a prior line of treatment for this clinical study was clarified as follows: **“Adjuvant therapy in the metastatic setting (administered following a surgical procedure) and investigational products are included in the definition of a prior line of treatment for the purposes of this study.”**

Purpose of Change: Administrative, to improve the clarity of the protocol.

18. Section 6.4.2.1, Clinical Protocol 391101; Section 6.5, Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Description of Change: Updated the total number of human subjects treated with imalumab up to the most recent data cut-off date (2015 JUL 01):

- “28 subjects” was updated to “48 subjects”.
- “30 Sep 2014” was updated to “2015 JUL 01”.

Purpose of Change: Administrative, in response to feedback from the MHRA (UK) and PEI (Germany).

19. Section 6.4.2.1.1, Safety Summary

Description of Change: Summarized the safety data for imalumab reported up to the most recent data cut-off date (2015 JUL 01). The following changes were made:

- Presented further details of the one SUSAR reported as of 2015 JUL 01 (MedDRA preferred term: alveolitis allergic).
- Presented more details of the cancer types treated in Cohorts 5, 7, 8 and 10 of Study 391101.
- Presented details of an additional SUSAR reported after the data cut-off date (2015 JUL 01) on 2015 SEP 16 (nausea, vomiting, and constipation).
- Presented summary of SAEs and related AEs that have occurred as of the 2015 JUL 01 cut-off date and added a cross-reference to the IB.

Purpose of Change: Safety, in response to feedback from the MHRA (UK) and PEI (Germany).

20. Section 8.2.1.1, Protocol 391401 Dose Escalation Scheme, Figure 1

Description of Change: Figure 1 was duplicated in error and a superfluous copy was included in the clinical trial protocol; the extra copy was deleted in this amendment.

Purpose of Change: Administrative, correction for clarity.

21. Section 8.2.3, Definition of Dose-Limiting Toxicity; Section 10.3.3.1, Study Drug Administration

Description of Change: Updated the protocol to provide reference for dose modifications that will be implemented in response to a dermatologic reaction (NCI CTCAE Grade 3 or higher, or considered intolerable) in subjects treated with panitumumab (Amgen Inc., 2015).

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

22. Sections 8.7.1.2, Leucovorin; 8.7.1.3, 5-Fluorouracil; 8.7.1.4, Panitumumab; 9.1, Inclusion Criteria; 10.3.2.3, Day 8 of Each Cycle

Description of Change: Labeling details updated to include “if applicable”.

Purpose of Change: Administrative.

23. Section 8.7.2.1 Imalumab; Section 8.7.3.1 Imalumab

Description of Change: Detailed information describing routine clinical practice for preparing products for injection was removed from the protocol and a reference to the Pharmacy Manual was added. The permissible time for vials of imalumab to be removed from storage prior to infusion was clarified as “7 hours (4 hours prior to aspiration and 3 hours after aspiration)”. Storage of product prior to administration was clarified that “Vials removed from storage to equilibrate to room temperature must not be removed from secondary packaging (original outer box), in order to protect product from light until administration.” The instructions for IV administration of imalumab were updated as follows: “The syringe may be hand-pushed for IV administration; alternatively, a syringe-driver pump may be used to actuate the syringe depending on the user/administrator’s comfort and/or preference. Considerations include: the amount of product to be infused, the size of the syringe used, the length of time to administer the product, and the user’s ability to deliver the product as indicated.”

Purpose of Change: Administrative, to update and clarify procedures for imalumab administration.

24. Section 8.7.2.3, Standard of Care Drugs; Section 8.7.3.3, Standard of Care Drugs

Description of Change: Added a recommendation that investigators should respect the contraindications in the SmPCs of the comparators and give consideration to the special warnings and precautions in the SmPCs of comparators.

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

25. Section 8.7.3.3, Standard of Care Drugs; Section 8.7.4.2.2, Arm B (Investigator Choice); Section 10.3.3.1.2, 5-Fluorouracil, Leucovorin, Panitumumab, and Standard of Care Administration

Description of Change: Reiterated that if subjects are to be treated with panitumumab as SoC they should not have a known history of keratitis, ulcerative keratitis or severe dry eye. Added a recommendation that investigators should advise subjects to minimize exposure to ultraviolet light (sunlight) following treatment with 5-FU or panitumumab, to be consistent with the advice given in the SmPCs for these products (Section 10.3.3.1.2 only).

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

26. Section 9.1, Inclusion Criteria

Description of Change: Minor update to inclusion criterion #8 to match exactly the equivalent inclusion criterion presented in the Synopsis (Section 3). Changed as follows:

- “Known KRAS, and NRAS mutation status (if unknown status for either of these genes and no archival tissue is available, a fresh tumor biopsy will be obtained)”.

Purpose of Change: Administrative, correction for protocol inconsistency.

27. Section 9.3, Withdrawal and Discontinuation

Description of Change: Added use of prohibited therapies as an additional withdrawal criterion.

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

28. Section 10.3, Screening and Study Visits

Description of Change: It was clarified that, at re-screening, results from assessments that were conducted within the previous 21 days can be reused, to avoid repetition of numerous Screening assessments.

Purpose of Change: Administrative, to improve the clarity of the protocol.

29. Section 10.3.1, Screening Assessments; Section 10.3.2, Baseline Assessments

(Cycle 1 Day 1, predose); Section 10.3.3.2, Day 1 of Each Cycle; Section 10.3.3.3, Day 8 of Each Cycle; Section 10.3.3.4 Day 15 of Each Cycle; Section 10.3.3.5, Day 22 of Each Cycle; Section 10.3.3.9 End of Study/Early Termination Visit; Section 20.2, Schedule of Study Procedures and Assessments: Parts 1 and 2 (Table 3); Section 20.2, Schedule of Study Procedures and Assessments: SoC Following Randomization (4-week Cycles or if Subject is on Best Supportive Care) (Table 4); Section 20.2, Schedule of Study Procedures and Assessments: SoC Following Randomization (3-week Cycles) (Table 5)

Description of Change: The protocol was updated to replace “IRT System telephone call” with “**Entry into IRT System**”, as this is a computer-based system and does not operate via the telephone. This assessment was also added to the End of Study/Early Termination study visit (Section 10.3.3.9).

Purpose of Change: Administrative, to improve the clarity of the protocol.

30. Section 10.3.1, Screening Assessments; Section 10.3.2 Baseline Assessments (Cycle 1 Day 1 predose); Section 20.2 Schedule of Study Procedures and Assessments: Parts 1 and 2 (Table 3)

Description of Change: Section 10.3.1 was split out into two distinct sections to describe separately the assessments and procedures to be conducted at Screening and Baseline. It was clarified that all Screening procedures should be performed within 28 days of first imalumab administration (C1D1). Use of the micro satellite instability technique for genetic testing was removed from the protocol. The timing of the Baseline Visit (Day -1) was changed; the Baseline Visit will now take place at C1D1. It was clarified that all questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D) should be administered and completed prior to the start of any assessments at Baseline (C1D1). The timing of the laboratory assessments immediately prior to Cycle 1 was clarified (either on Day -1 or on Day 1 predose).

Purpose of Change: Administrative, to improve the clarity of the protocol.

31. Section 10.3.3.1 Study Drug Administration

Description of Change: It was clarified that if treatment with 5-FU/LV or panitumumab is interrupted due to an AE, and there are no concurrent safety concerns regarding imalumab, treatment with imalumab may be continued while treatment with 5-FU/LV or panitumumab is interrupted.

Purpose of Change: Administrative, to improve the clarity of the protocol.

32. Section 10.3.3.2 Day 1 of Each Cycle

Description of Change: Updated to clarify that the assessments and procedures to be conducted at Baseline (C1D1) predose are described in Section 10.3.2.

Purpose of Change: Administrative, to improve the clarity of the protocol.

33. Section 10.3.2 Baseline Assessments (Cycle 1 Day 1, predose); Section 10.3.3.2 Day 1 of Each Cycle; Section 10.3.3.3 Day 8 of Each Cycle; Section 10.3.3.4 Day 15 of Each Cycle; Section 10.3.3.5 Day 28 of Each Cycle

Description of Change: The timing of the collection of blood samples for PK (imalumab plasma level) and PD biomarkers (oxMIF and total MIF) analyses was clarified.

Purpose of Change: Administrative, to improve the clarity of the protocol and for consistency with Table 6.

34. Section 10.3.3.3, Day 8 of Each Cycle

Description of Change: Corrected minor typographical error.

- “2” was removed from “Vital signs measurement should be recorded within 30 minutes of completion of the imalumab injection~~2~~”.

Purpose of Change: Administrative, correction for clarity.

35. Section 10.3.3.7 Day 28 (Cycle 2 and Every Other Cycle); Section 11.2, Antitumor Effect – Solid Tumors

Description of Change: The timing of tumor measurements by CT or MRI scans was clarified (every 8 weeks) for subjects receiving SoC in 3-weekly treatment cycles. As these subjects will not have a Day 28 in their treatment cycles, the study day of these assessments will vary from cycle to cycle. Day 22 will be the first day of the next treatment cycle in subjects receiving SoC in 3-weekly treatment cycles. The timing of the Baseline tumor measurements was clarified as being within 28 days prior to first imalumab administration (C1D1) rather than 28 days prior to screening (Section 11.2).

Purpose of Change: Administrative, to improve the clarity of the protocol.

36. Section 10.3.3.8 Day 29 = Day 1 of the Next Cycle

Description of Change: Section 10.3.3.8 (original numbering) was deleted from the protocol: “Section 10.3.3.8 Day 29 = Day 1 of the Next Cycle

Refer to procedures as outlined in Section 10.3.3.2.”

Purpose of Change: Administrative, to improve the clarity of the protocol.

37. Section 10.3.3.8 End of Study/Early Termination Visit, Section 10.3.3.9 Safety Follow-up Visit

Description of Change: Section 10.3.2.8 (original numbering) was split out into two distinct sections to describe separately the assessments and procedures to be conducted at the End of Study/Early Termination Visit and Safety Follow-up Visit. It was clarified that at both of these visits all questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D) should be administered and completed prior to the start of any assessments.

Purpose of Change: Administrative, to improve the clarity of the protocol.

38. Section 10.3.3.8, End of Study/Early Termination Visit; Section 10.3.3.9, Safety Follow-up Visit; Section 11.2, Antitumor Effect - Solid Tumors; Section 20.2, Schedule of Study Procedures and Assessments: Parts 1 and 2 (Table 3); Section 20.2, Schedule of Study Procedures and Assessments: SoC Following Randomization (4-week Cycles or if Subject is on Best Supportive Care) (Table 4); Section 20.2 Schedule of Study Procedures and Assessments: SoC Following Randomization (3-week Cycles) (Table 5)

Description of Change: The tumor measurements to be conducted at the End of Study/Early Termination Visit and Safety Follow-up Visit were clarified as follows: “A tumor measurement should be obtained at the End of Study/Early Termination visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan; no additional scans will be required if disease progression is confirmed at this visit. A tumor measurement should be obtained at the Safety Follow-up visit, if no disease progression was confirmed previously and this visit occurs > 4 weeks after the last scan.

Purpose of Change: Administrative, to improve the clarity of the protocol.

39. Section 10.4, Medications and Non-Drug Therapies

Description of Change: Updated list of prohibited medications and changed language around discontinuation of subjects who receive prohibited medications or non-drug therapies. In addition, corrected minor typographical error.

- “Brivudin, sorivudine and other nucleoside analogues must be avoided in subjects who receive treatment with 5-FU” was added
- “Live vaccines must be avoided for 6 weeks following last dose of imalumab” was added
- “A subject who has taken any of these medications or received any of these non-drug therapies **may** be discontinued” was changed to “A subject who has taken any of these medications or received any of these non-drug therapies **must** be discontinued”
- Changed “CID1” to “C1D1”

Purpose of Change: Safety, in response to feedback from the MHRA (UK); Administrative, correction of typographical error for clarity.

40. Section 11, ASSESSMENT OF EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND GENETIC TESTING

Description of Change: The wording of the section heading was updated to take into consideration the additional genetic testing added to the protocol.

Purpose of Change: Administrative, for consistency with other updated sections of the protocol.

41. Section 11.3, Genetic Testing

Description of Change: Genetic testing for the MSI phenotype was removed from the protocol. It was specified that genetic testing for KRAS/NRAS mutation needs to be performed early enough to allow randomization within 4 weeks; however, if KRAS mutation status is known, it is permissible for the subject to start treatment while NRAS testing is pending.

Purpose of Change: Administrative, for consistency with other updated sections of the protocol.

42. Section 11.4, Tumor-associated Biomarkers

Description of Change: Details of the timing and procedures for assessing tumor-associated genetic biomarkers were added to the protocol.

Purpose of Change: Administrative, for consistency with other updated sections of the protocol.

43. Section 12.1.1, Definitions

Description of Change: To ensure complete clarity of the instructions for assessing events relating to disease progression, updated this section as follows: “Events relating to clinical deterioration due to disease progression as a result of the underlying malignancy are not to be considered or analyzed as AEs (or SAEs), but **will be recorded on the CRF.**”

Purpose of Change: Administrative.

44. Section 12.1.1.4, Unexpected Adverse Events

Description of Change: The statement “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation” was changed to “**The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.**”

Purpose of Change: Safety, in response to feedback from the MHRA (UK) and PEI (Germany).

45. Section 12.1.2, Assessment of Adverse Events

Description of Change: The permitted window for the follow-up of each TEAE was amended to ± 7 days, instead of ± 2 days.

Purpose of Change: Administrative correction.

46. Section 12.1.2.3, Safety Reporting

Description of Change: As an eCRF will be used for this study, this section was included in the protocol per the instructions in the Baxalta clinical study protocol template. Section 12.11, Safety Reporting, was deleted to avoid redundancy with Section 12.1.2.3.

Purpose of Change: To maintain consistency with current Baxalta protocol template.

47. Section 12.2, Urgent Safety Measures

Description of Change: Revised this section of the protocol to indicate that, in addition to the responsible EC, Regulatory Authorities must be informed of any urgent safety measures. Text in bold was added:

- “The sponsor will also ensure the responsible ethics committee (EC) **and the relevant competent authorities are** notified **(in writing, if applicable)** of the urgent **safety** measures taken in such cases according to local regulations.”

Purpose of Change: Safety, in response to feedback from the MHRA (UK).

48. Section 13.2 Datasets and Analysis Cohorts

Description of Change: The “FAS Population” was changed, and is now referred to consistently as the “FAS”. The definition of the FAS was changed as follows: “The FAS will include all subjects who 1) received at least 1 administration of IP, and 2) have 1 post-baseline tumor response assessment based on RECIST v1.1 **or died within 18 weeks of the start of treatment.**”

Purpose of Change: Administrative.

49. Section 13.4.4.2, Safety Outcome Measures

Description of Change: The analysis that will be conducted for AEs was updated as follows: “Adverse events will be grouped by system organ class, ~~high level term (HLT), and standardized MedDRA query (SMQ).~~”

Purpose of Change: Administrative.

50. Section 15.4, Safety Monitoring

Description of Change: Section 12.10 (previous numbering), Safety Monitoring, and Section 16.4, Data Safety Monitoring, were merged in a new section (Section 15.4) to minimize repetition and as per the instructions in the Baxalta clinical study protocol.

Purpose of Change: To maintain consistency with current Baxalta protocol template.

51. Section 20.1, Study 391401 Schematic, Figure 2

Description of Change: Figure 2 was duplicated in error and a superfluous copy was included in the clinical trial protocol; the extra copy was deleted in this amendment.

Purpose of Change: Administrative, correction for clarity.

52. Section 20.2, Schedule of Study Procedures and Assessments: Parts 1 and 2 (Table 3)

Description of Change: Table 3 was updated to reflect all of the changes made elsewhere in the protocol, namely:

- Screening was extended from 21 days (3 weeks) to 28 days (4 weeks)
- The Baseline Visit was moved from Day -1 to coincide with Day 1
- The End of Study/Early Termination Visit procedures were separated from the Safety Follow-up Visit procedures
- The duration of the visit windows was extended from ± 1 days to ± 2 days (with the exception of the ± 7 -day window for Safety Follow-up Visit)
- The footnotes for the vital signs, ECG and laboratory assessments were updated for consistency with other sections of the protocol. The timing of the laboratory assessments immediately prior to Cycle 1 was clarified (either on Day -1 or on Day 1 predose). The timing of the 12-lead ECG assessments at Screening and on Day 1 (Baseline, C1D1) was clarified.
- BRAF/MIS components of the genetic testing were removed from the protocol
- Blood/urine sample collection for assessment of genetic biomarkers from cfDNA was added to the schedule of assessments and a footnote added
- Abbreviations were redefined according to updated Table 3 and footnotes
- The timing of the Safety Follow-up Visit was specified (30 ± 7 days after last dose of study treatment)
- It was specified that genetic testing for KRAS/NRAS mutation needs to be performed early enough to allow randomization within 4 weeks; however, if KRAS mutation status is known, it is permissible for the subject to start treatment while NRAS testing is pending.
- It was specified that baseline CT or MRI scans can be accepted within 28 days prior to first imalumab administration (C1D1), repeated every 2 cycles (8 weeks) with a 7-day window is permitted for all imaging studies for tumor measurement purposes
- The timing of the collection of blood samples for PK (imalumab plasma level) and PD biomarkers (oxMIF and total MIF) analyses was clarified and harmonized with Table 6

Purpose of Change: Administrative, for consistency with the updates made throughout this clinical study protocol.

53. Section 20.2, Schedule of Study Procedures and Assessments: SoC Following Randomization (4-week Cycles or if Subject is on Best Supportive Care) (Table 4); Schedule of Study Procedures and Assessments: SoC Following Randomization (3-week Cycles) (Table 5)

Description of Change: Two new schedules of assessments were added to the clinical study protocol: Table 4 and Table 5 describe the assessments and procedures for subjects receiving SoC on 4-week and 3-week treatment cycles, respectively.

Purpose of Change: Administrative, to provide greater clarity to investigators.

54. Section 20.2, Schedule of Pharmacokinetic and Pharmacodynamic Sample Collections (Parts 1 and 2) for Subjects Receiving Imalumab Treatment (Table 6)

Description of Change: Table 6 was updated to include the blood sample taken at Screening (Days -28 to -1) for PK and PD assessments. The acceptable time windows for the collection of blood samples at 24 hours (\pm 4 hours after infusion) and at 72 hours (\pm 8 hours after infusion) were also included.

Purpose of Change: Administrative, for consistency with other sections of the updated protocol.

55. Section 20.2, Blood Volumes (Parts 1 and 2) for Lab Tests and PK/PD for Subjects Receiving Imalumab Treatment (Table 7)

Description of Change: Table 7 was updated to include the blood samples taken at Screening (Days -28 to -1) for hematology/blood chemistry/coagulation and PK/PD assessments. The timing of taking these blood samples at each subsequent treatment cycle was corrected. Footnote b was deleted (not relevant to the contents of this table).

Purpose of Change: Administrative, for consistency with other sections of the updated protocol.

56. Section 20.2, Blood and Urine Volumes (Parts 1 and 2) for Optional Genetic Biomarkers cfDNA Analysis for Subjects Receiving Imalumab Treatment (Table 8)

Description of Change: Table 8 was included in the updated protocol to describe the volumes of blood and urine samples that will be taken for the genetic biomarker analyses at Screening (Days -28 to -1), Cycle 1 Day 28, every other cycle and at the End of Study/Early Termination Visit.

Purpose of Change: Administrative, for consistency with other sections of the updated protocol.

57. Section 21, References

Description of Change: Addition of new references per new information included in the following sections:

- Section 6.1.4: Misale et al 2012 (Ref #22); Thierry et al 2014 (Ref #23); Haber and Velculescu 2014 (Ref #24); Tóth et al 2016 (Ref #25); Patel and Karapetis 2013 (Ref #26); Spindler et al 2012 (Ref #27); Kapur 2012 (Ref #28)
- Section 6.1.5.4: Sastre et al, 2015 (Ref #32); Price et al, 2014 (Ref #33)
- Section 8.2.3: Amgen Inc., 2015 (Ref #34).

Purpose of Change: Administrative, a consequence of feedback from the MHRA (UK), as well as to provide more background information on the genetic biomarkers analyses.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: BAX69 (Imalumab)

STUDY TITLE: A Phase 2a Randomized, Open-Label Study to Assess the Safety, Tolerability, and Efficacy of BAX69 in Combination with 5-FU/Leucovorin or Panitumumab versus Standard of Care in Subjects with Metastatic Colorectal Cancer

PROTOCOL IDENTIFIER: 391401

CLINICAL TRIAL PHASE 2a

AMENDMENT 5 (GLOBAL): 2016 MAY 09

Replaces Amendment 2 (GLOBAL): 2015 JUL 13

ALL VERSIONS:

Amendment 4 (Germany Version): 2015 DEC 16

Amendment 3 (UK Version): 2015 OCT 02

Amendment 2 (GLOBAL): 2015 JUL 13

Amendment 1 (GLOBAL): 2015 MAR 06

Original (GLOBAL): 2014 DEC 10

OTHER ID(s)

EudraCT Number: 2015-000896-28

IND NUMBER: 112850

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, CTA, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator

Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative

Date

PPD [REDACTED], MD, PPD [REDACTED], Clinical Development