STATISTICAL ANALYSIS PLAN

Imalumab (BAX69)
PHASE 2a

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

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1. INTRODUCTION AND OBJECTIVES

The purpose of this study, in subjects with progressive measurable metastatic colorectal cancer (mCRC), is as follows:

- 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.

The statistical analysis plan outlines the methods for the planned final analysis in the protocol. As the study will continue to be on-going, an additional analysis addendum to the study report will be performed at the completion of the study.

1.1 Study Objectives

1.1.1 Primary Objectives

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)

1.1.2 Secondary Objective(s)

1.1.2.1 Efficacy

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 line

2. 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 line

1.1.2.2 Safety

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

1.1.2.3 Pharmacokinetics

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

1.1.2.4 Health-related Quality of Life

- To compare health related 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.

1.1.3 Exploratory Objectives

1.1.3.1 Pharmacodynamics

The exploratory PD objective of the study is to characterize oxidated 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.

1.1.3.2 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.

1.1.3.3 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

2. STUDY DESIGN

This study is Phase 2a, randomized, open-label study to assess the safety, tolerability, and efficacy of imalumab in combination with 5-FU/LV or panitumumab versus Standard of Care (SOC) in subjects with metastatic colorectal cancer.

This 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):

- 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, , 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.

- 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, NRAS mut tumors) or imalumab + panitumumab (KRAS wt and NRAS wt tumors) (Arm A) or SoC per investigator choice (Arm B).

For all subjects in Parts 1 and 2, treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent.

Part 1: Safety Run-in

For each combination, subjects will be enrolled into 2 sequential cohorts, with a minimum of 3 and a maximum of 6 subjects per cohort.

For each combination, enrollment will proceed according to the following rules based on the occurrence of dose-limiting toxicities (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 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 will not be open to enrollment and the DRC will decide if a lower dose level will be explored.

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.

DLT Definition

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 ≥ Grade 3 non-hematologic toxicity excluding:
    - Mucositis/stomatitis of Grade 3 that resolves to Grade 1 or less with supportive measures within 7 days
    - Diarrhea of < 3 days duration following adequate and optimal therapy
    - Nausea and vomiting of < 3 days duration with adequate and optimal therapy
    - Fatigue of < 7 days duration following initiation of adequate supportive care
    - Alopecia
    - Any single laboratory value out of the normal range that has no clinical significance and that resolves to ≤ 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:
  - Grade 4 neutropenia lasting for ≤ 5 days and not accompanied by fever
  - 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 study in which subjects will 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, biostatistics, clinical care and research will review accumulating safety data. The composition, activities, and responsibilities of the DSMB are described in further detail in the DSMB Charter.

2.1 Study Population

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 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2.

2.2 Inclusion and Exclusion Criteria

2.2.1 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. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2
11. Adequate hematological function, defined as:
    a. Platelet count ≥ 100,000/µL
    b. Prothrombin time and activated partial thromboplastin time (aPTT) < 1.5 times the upper limit of normal (ULN)
    c. Absolute neutrophil count (ANC) ≥ 1,000/µL
    d. Hemoglobin ≥ 9 g/dL, without the need for transfusion in the 2 weeks prior to screening
12. Adequate renal function, defined as serum creatinine ≤ 2.0 times ULN and creatinine clearance > 50 mL/min or estimated glomerular filtration rate> 50 mL/min/1.73 m^2
13. Adequate liver function, defined as:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN for subjects without liver metastases, or ≤ 5 times ULN in the presence of liver metastases
    b. Bilirubin ≤ 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 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.

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

2.2.2 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 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 ≥ 160 mmHg and/or diastolic blood pressure ≥ 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 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

2.3 Sample Size and Power Calculations

The final sample size of Part 1 (Safety Run-in) is dependent on the pre-stated rules for dose escalation. 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 7.5 mg/kg and 10 mg/kg imalumab dose level). Non-evaluable subjects will be replaced to meet study objectives.

The sample size of Part 2 (Exploratory Phase 2a) 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 (a constant hazard ratio 0.565), and using a one-sided log-rank test with 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 approximately 22 subjects in each of the 2 imalumab-containing treatment arms (imalumab + panitumumab and imalumab + 5-FU/LV) and in the control arm (SoC).

2.4 Randomization

There is no randomization in Part 1. In Part 2, randomization in permutated blocks 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.

2.5 Blinding/Unblinding

This is an open-label study.

2.6 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 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 independent ethics committee/institutional review board (IEC/IRB) promptly and provide the reason for the interruption or termination.

Study completion is estimated to occur when 75% of OS events have been reported.

There are no specific statistical stopping rules defined for this study.

2.7 Study Assessments

A schedule of assessments is provided in Section 16.1.

2.8 Data Monitoring Committee

The composition, activities, and responsibilities of the DSMB are described in further detail in the DSMB Charter.

3. STUDY OUTCOME MEASURES

3.1 Efficacy Outcome Measures

3.1.1 Primary Efficacy Outcome Measure

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.

3.1.2 Secondary Efficacy Outcome Measures

The secondary outcome measures are:

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

3.2 Safety Outcome Measures

3.2.1 Primary Safety Outcome Measures

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

3.2.2 Secondary Safety Outcome Measures

- Occurrence of serious adverse events (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

3.3 Immunogenicity Outcome Measures

- Occurrence of binding and/or neutralizing anti-imalumab antibodies

- Incidence and severity of infusion reactions after imalumab

3.4 Pharmacokinetic Outcome Measures

The PK outcome measure is the plasma concentrations of imalumab. Imalumab plasma PK will be characterized using a population PK modeling approach, in combination with data from other studies. The population PK modeling approach will be described and reported in separate documents.

3.5 Quality of Life Outcome Measures

The QoL outcome measures are derived from answers to the EORTC QLQ-C30 questionnaire.

3.6 Exploratory Outcome Measures

The exploratory PD outcome measures include plasma levels of oxidated macrophage migration inhibitory factor (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.

4. ANALYSIS SETS

4.1 Full Analysis Set

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 study drug, and 2) have 1 post-baseline tumor response assessment based on RECIST v1.1, or died within 18 weeks of the start of treatment.

The proposed derivation of PFS (Section 7.1.1) indicates that subjects who miss 2 planned tumor assessments will be censored at the last tumor assessment before the

missed assessments. For this study, the exact time period that identifies that 2 tumor assessments have been missed will be defined as twice the protocol-defined time between scans (8 weeks) + the protocol allowed visit window (1 week) (ie, 2 * 8 + 1 = 18 weeks).

4.2 Safety Analysis Set

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

5. STATISTICAL CONSIDERATIONS

The numerical data will be summarized with n, mean, SD, min, max, median, Q1, and Q3. Categorical data will be summarized with n and percentages.

There are no multiplicity adjustments in this exploratory Phase 2A study.

All secondary and exploratory endpoints are considered supportive and any statistical tests comparing treatments will be made without adjustment for multiplicity. The resulting p-values from these supportive analyses will be interpreted descriptively as summarizing the weight of evidence for a treatment difference and may suggest avenues for further exploratory analyses or generate formal hypotheses to be tested in future trials.

5.1 Interim Analyses

An interim analysis was to be implemented for planning purposes but was removed from the plan (See Section 5.5).

5.2 Handling of Missing, Unused, and Spurious Data

Regarding missing data in AE records:

- Handling of unknown causality assessment:
  - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as “related”.
- Handling of unknown toxicity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, the subject will be counted under the most severe toxicity grade reported for that AE.
  - If a subject experiences an AE and the toxicity grade was not provided, the toxicity grade of this AE should be counted as “unknown”. A row or column labelled “Unknown” should be inserted for those AEs in tables where AEs are summarized by toxicity grade.

For lab values that are above or below the limit of quantitation and are reported as "<" or ">" the assay limit, the assay limit will be used for calculation of summary statistics, except for PK parameters which will be specified in a separate document.

5.3 Definition of Baseline

Baseline will be defined as the last assessment before the date and time of first administration (C1D1) of imalumab or SoC. For subjects who have not received any study drug, the baseline will be the last assessment performed at Screening, Baseline, or C1D1.

If more than one baseline scan is recorded then measurements from the one that is closest and prior to the date of randomization will be used to define the baseline.

5.4 Definition of Treatment Groups

Data will be presented for the cohorts in Part 1 and Part 2 of this study which are listed in Table 1.

The dose of imalumab selected for Part 2 is 10 mg/kg. Subjects from Part 1 and Part 2 who received the 10 mg/kg dose will be combined for some analyses of safety and efficacy. The Part 1 and 2 analyses will indicate that subjects in 10 mg/kg cohorts in Part 1 will be combined with the Part 2 cohorts that received the same treatment.

Data from the cohorts receiving 7.5 mg/kg imalumab in Part 1 will not be included in the integrated Part 1 and 2 analyses.

Table 1: Combination and Pooled Treatment Groups

Study Part	Study Cohort	Integrated Treatment Group
Part 1	Imalumab 7.5 mg/kg + 5-FU/LV	
Part 1	Imalumab 7.5 mg/kg + Panitumumab	
Part 1	Imalumab 10.0 mg/kg + 5-	Imalumab 10.0 mg/kg + 5-

	FU/LV	FU/LV
Part 2	Imalumab 10.0 mg/kg + 5-FU/LV	
Part 1	Imalumab 10.0 mg/kg + Panitumumab	Imalumab 10.0 mg/kg + Panitumumab
Part 2	Imalumab 10.0 mg/kg + Panitumumab	
Part 2	SoC Mutated	SoC Mutated
Part 2	SoC Wildtype	SoC Wildtype

5.5 Changes from the Planned Statistical Analysis in Protocol

In the protocol	In the SAP	Justification
An interim analysis will be implemented for planning purposes when 33 PFS events have been observed.	An interim analysis will not be preformed	The interval between observing 33 PFS events and observing the 48 PFS events needed for final analysis was short. Therefore, interim analysis was not performed.
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).	The PFS will be defined as time between randomization and tumor progression (per RECIST v1.1) or death from any cause (see Section 8.4.1).	To align the starting point of PFS and OS.

6. STUDY SUBJECTS

6.1 Disposition of Subjects

A summary of patient enrollment will display the number of patients who were screened, screen failures, randomized and treated. Subject disposition will summarize the number (%) of subjects that comprised each analysis population. A listing of subject disposition, including analysis populations, will be created.

6.2 Demographic and Baseline Characteristics

The following baseline data will be summarized and listed for the FAS and Safety Analysis Set: age (years), sex, race, ethnicity, country, Eastern Cooperative Oncology Group (ECOG) performance status, left ventricular injection fraction (LVEF), height (cm), weight (kg), and BMI (kg/m^2). Demographics and baseline characteristics will be summarized for study cohort and integrated treatment group.

6.3 Medical History

Disease history will be summarized for the Safety Analysis Set for study cohort and integrated treatment groups. Disease history will include type of colorectal cancer, stage at initial diagnosis, histological subtypes, time since primary diagnosis (years), diagnosis confirmation type (histologically or cytologically), KRAS/NRAS status, TNM staging at informed consent, and sites of distant metastatic disease.

Duration from initial diagnosis (years) diagnosis will be calculated at the date of informed consent using the following formula:

- Duration from initial diagnosis (years): (Date informed consent signed – Date of initial diagnosis) / 365.25.

Medical history will be summarized for the Safety Analysis Set for study cohort. Medical conditions collected will be mapped by the Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term. For summary tables, a subject will be counted only once per body system and preferred term. Disease and medical history will be included in data listings.

6.4 Prior Therapies and Medications

Prior therapies and medications include prior cancer-related surgeries, radiotherapies, and medications as well as other general medications taken prior to the first dose in Cycle 1. Prior cancer-related surgeries, radiotherapies, and medications are collected on

specifically-designed CRFs. Other prior medications will be recorded on the concomitant medications eCRF and coded using the WHO Drug Dictionary version September 2015. Medication start dates will be used to identify which medications entered on the concomitant medications eCRF could be considered as prior medications. Prior cancer-related surgeries, radiotherapies, and medications will be summarized for the Safety Analysis Set for study cohort and integrated treatment group.

Prior medications will be tabulated by WHO Preferred Name for the Full Analysis Set and will be included in a general concomitant medication listing that will identify prior medications. The number and percent of subjects who experienced prior cancer-related surgeries and radiotherapies will be tabulated along with other cancer-related medications tabulated by WHO Preferred Name. Prior medications will be summarized for the Safety Analysis Set for study cohort and integrated treatment group. Prior cancer-related surgeries, radiotherapies, and medications will also be included in data listings.

6.5 Concomitant Medications

Concomitant medications are defined as medications taken after the start of study treatments. Concomitant medications will be recorded on the eCRF and coded using the WHO Drug Dictionary version September 2015. Medication start and end dates will be used to identify which medications entered on the concomitant medications eCRF could be considered as concomitant medications. Concomitant medications will be summarized for the Safety Analysis Set for study cohorts and integrated treatment groups. All concomitant medications will be included in by-subject data listings.

6.6 Protocol Deviations

A protocol deviation summary will be provided. The number and percent of subjects with protocol deviations will be summarized by severity and category for the Part 1 and 2 safety analysis set by study cohort. The protocol deviation categories are:

1. Informed Consent Criteria
2. Eligibility and Entry Criteria
3. Concomitant Medication Criteria
4. Laboratory Assessment Criteria
5. Study Procedures Criteria
6. Serious Adverse Event Criteria
7. Randomization Criteria
8. Visit Schedule Criteria
9. IP Compliance
10. Efficacy Criteria
11. Administrative Criteria

12. Source Document Criteria
13. Regulatory or Ethics Approvals Criteria
14. Other Criteria

All protocol deviations will be included in by-subject data listings.

7. EFFICACY EVALUATION

7.1 Analysis of Primary Efficacy Outcome Measure

7.1.1 Derivation of Primary Efficacy Outcome Measure

The revised RECIST guidelines (Eisenhauer et al., 2009) will be used to determine disease progression. Date of disease progression is the earliest date of the imaging method to determine disease progression.

For an individual subject, the imaging method used to measure tumor burden at baseline should be used for each future tumor assessment. Baseline tumor measurements and identification of target lesions may be based on imaging obtained within 28 days prior to screening. Scheduled tumor response assessments must be interpreted prior to the start of the next treatment cycle.

Date of Progression will be derived as follows:

1. For progression based on new lesion(s), the date of progression is the first scan date on which the new lesion is detected.

2. For progression based on target lesions, , the date of progression is the date of the initial scan of target lesions showing >20% increase in the sum of diameters of target lesions;

3. For progression based on non-target lesions, the date of progression is the date of the first scan that indicated unequivocal progressive disease of existing non-target lesions.

The date of progression will be the earliest date among dates described above.

For tumor response evaluation from assessments on which multiple scans are done on different dates and no evidence of progression is indicated, the latest date of all scans will be considered as the evaluation date showing no evidence of progression for that assessment. In cases where one or more lesions (target or non-target lesions identified at baseline) do not have an assessment at a given post-baseline evaluation, the assessment

for tumor response for that visit will be considered "not evaluable (NE)" unless disease progression is noted.

PFS is defined as the time between randomization 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.

This will be regardless of whether the subject receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the subject progresses or dies after two or more missed tumor assessments, the subject will be censored at the time of the latest evaluable RECIST assessment. If the subject has no evaluable visits or does not have baseline data they will be censored at 1 day unless they die within two visits of baseline. For this study, the exact time period that identifies that two tumor assessments have been missed will be defined as twice the protocol-defined time between scans + the protocol allowed visit window. RECIST assessments are scheduled to occur every other cycle, ie, every 8 weeks ± 1 week. If tumor scans indicate progression or the subject dies more than 2*9 weeks=18 weeks (126 days) after the previous tumor assessment, the subject will be censored on the date of the assessment prior to progression or death.

Table 2 below specifies the date of disease progression or censoring rules that will be carried out for the PFS analysis:

Table 2: Date of Progression or Censoring for Progression-free Survival

Situation	Date of Disease Progression or Censoring	Outcome
Alive with no post-baseline assessments for tumor response	Treatment start date	Censored
Disease progression or death after two or more consecutive missed tumor response assessments	Date of last scan for tumor assessment showing no evidence of disease progression that is before the first missed visit.	Censored
Not known to have progressed or died according to data in the database as of data-cut-off	Date of last scan for tumor assessment showing no evidence of disease progression	Censored
Withdrawal from the study or loss to follow-up	Date of last scan for tumor assessment prior to withdrawal or loss to follow-up	Censored
Disease progression reported on multiple response assessments	Earliest Date of Progression as defined in this Section	Progressed
Death without Disease Progression	Date of death	Progressed

7.1.2 Analysis Methods for the Primary Efficacy Outcome Measure

Progression-free survival in the Part 2 treatment groups will be compared with a 1-sided log-rank test. The log-rank will be the primary assessment. Kaplan-Meier (KM) median PFS times and their 95% confidence intervals, estimates of first and third quartiles, as well as KM curves will be summarized by treatment group. A Cox regression model will be used to compare the hazard rate between the two treatment groups without stratification. A single hazard ratio and its 95% confidence interval will be calculated.

Results of tumor scans and related response assessments for subjects enrolled in this study will be included in by-subject data listings.

7.2 Analysis of Secondary Efficacy Outcome Measure

7.2.1 Derivation of Secondary Outcome Measures

7.2.1.1 Overall Survival

Overall survival is defined as the time from randomization until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Last date known to be alive will be obtained from the survival follow-up CRF. If that CRF hasn't been completed the following CRF fields will be used to determine the last date known to be alive:

- Dates of administration of chemotherapy and study drug
- Laboratory specimen collections dates
- PK/PD blood sampling dates
- CT and/or MRI scan dates
- Date of vital sign assessments
- Date of ECG assessments
- Date of contact on the survival follow-up CRF
- Date of Quality of Life assessments
- Start and stop dates for concomitant treatments
- Date of onset and resolution of AEs
- Completion/termination date.

Overall survival will be analyzed with the methods used for the analysis of PFS.

7.2.1.2 Overall Response Rate

Tumor response will be assessed by the investigator based on the revised RECIST guidelines (Version 1.1) at each radiographic assessment. Radiological exams are required every 8 weeks (±7 days) starting from date of randomization without delays for toxicity until protocol-defined disease progression is noted. Results based upon scans performed after start of new anti-cancer therapy will be excluded when calculating the best overall response. Objective response rate will be defined as the proportion of subjects with a complete response (CR) or a partial response (PR) per RECIST based upon the best response as assessed by the investigator; confirmation of response is not required. Clinical benefit rate (CBR) will be defined as the proportion of subjects with a complete response (CR), a partial response (PR), or stable disease (SD) per RECIST based upon the best response as assessed by the investigator. The analysis of ORR and CBR will be performed using Fisher's exact test to compare the relative rate of subjects with an objective response in the treatment groups without stratification. Clopper-Pearson exact 2-sided 95% confidence limits will be calculated for the proportion of subjects with ORR in each arm.

Since the presence of measurable disease is an inclusion criterion, the denominator for the rate will be the number of subjects in the FAS. In addition to representing ORR and CBR, the best overall response (BOR) using response categories CR, PR, SD, progressive disease (PD), and not evaluable (NE) will be tabulated. The proportion of subjects in each response category will be calculated for the study cohorts and the integrated treatment groups.

Subjects who do not have any post-baseline tumor assessment will be counted under the category Not Evaluable (NE).

7.3 Sensitivity Analyses

A sensitivity analysis will be conducted for PFS. The calculation of PFS will be the same as described in Section 7.1.1 except that subjects will also be censored at the latest tumor assessment prior to the start of a new anti-cancer therapy.

If any subjects are censored because they missed 2 tumor assessments, a second sensitivity analysis will be conducted to include these subjects as events. Otherwise, the calculation of PFS will be the same as described in Section 7.1.1.

A third sensitivity analysis will include subjects in Part 1 cohorts and be summarized by integrated treatment group.

The same statistical analysis methods used for the primary analysis of PFS, ie, log-rank test and Cox regression, will be used for all of these sensitivity analyses.

The best % change from baseline in target tumor diameters will be presented for each subject in a waterfall plot by study cohort.

8. SAFETY EVALUATION

8.1 Analysis of Primary Safety Outcome Measure

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 RP2D will be defined as the highest dose level examined at which < 33% of evaluable subjects experience a DLT during the first treatment cycle.

8.2 Extent of Exposure

The following variables will calculated:

- Exposure duration (days): date of last dose – date of first dose (C1D1) + 7, 7 is added to exposure duration to account for the 7-day rest period between imalumab administrations.
- Number of cycles: Total number of complete or partial treatment cycles the subject received.
- Number of Subjects with dose interrupted/ dose reduction

For imalumab, the following parameters will be calculated:

- Cumulative dose (mg): Total actual dose (mg) the subject received across all cycles, defined as the sum of actual dose (mg) received across all cycles.
- Calculated cumulative dose level (mg/kg): Cumulative dose (mg) divided by the average weight (kg) across all cycles.
- Dose intensity (mg/kg/week): {Calculated cumulative dose level (mg/kg) / (exposure duration (days)} x 7
- Expected dose intensity (mg/ kg/week): 7.5 or 10 mg/kg/week based on treatment arm
- Relative dose intensity (%): ((Dose intensity) / (expected dose intensity)) × 100.

8.3 Adverse Events

Adverse events (AE) will be coded by System Organ Class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. AE severity will be based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade (version 4.03).

A treatment-emergent AE (TEAE) is defined as 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. An AE that was present at treatment initiation, but resolved and then reappeared while the patient was on treatment, is a TEAE (regardless of the intensity of the AE when the treatment was initiated). If the start date of an AE is unavailable or incomplete, the AE CRF asks the subject/investigator to identify whether it occurred before the first treatment, during treatment, within 24 hours after the last treatment, or more than 24 hours after the last treatment. This information will used to determine if the AE will be considered as TEAE, when necessary. If the start time of the AE is provided, then the AE start date and time will be used to classify the AE as TEAE or not. If the start time is not provided and the AE occurs on the same day of first study drug administration (C1D1) then the AE will be classified as TEAE.

Adverse event data will be descriptively evaluated by treatment arm and for overall subjects. Incidence of TEAEs by MedDRA SOC, preferred term, and relationship (Related/Not Related) to study drug will be summarized based on the safety population. Adverse event incidence rates will be summarized with frequency of events, frequency of subjects affected and percentage (based on # subjects affected).

For subject level summaries, subjects with multiple occurrences of events with the same preferred terms and SOC will be counted once at the highest Grade and the strongest relationship to study drug for each preferred term, and system organ class.

Adverse events that are reported as possibly or probably related to study drug will be counted as related to study drug. Adverse events that are reported as unlikely related and unrelated will be summarized as not related. AEs with a missing relationship will be considered "Related" for this summary.

The adverse events summaries listed in Table 3will be provided for study cohort, integrated treatment group, and totals for the table for the safety analysis set:

Table 3: AE tables produced for treatment with and without stratification

AE Summary	Study Cohort	Integrated Treatment Group

AE Summary	Study Cohort	Integrated Treatment Group
TEAEs summary	Y	Y
TEAEs by System Organ Class and Preferred Term	Y	Y
TEAEs by Preferred Term and by Descending Incidence	Y	N
TEAEs by System Organ Class and Preferred Term and CTCAE Grade	Y	N
Grade 3 or Higher TEAEs by System Organ Class and Preferred Term	Y	N
Serious TEAEs by System Organ Class and Preferred Term	Y	Y
Non-Serious TEAEs by System Organ Class and Preferred Term and by Descending Incidence	Y	N
Serious TEAEs by System Organ Class and Preferred Term and CTCAE Grade	Y	N
Treatment-Related TEAEs by System Organ Class and Preferred Term	Y	N
Treatment-Related TEAEs by Preferred Term and by Descending Incidence	Y	Y
Treatment-Related TEAEs by System Organ Class and Preferred Term and CTCAE Grade	Y	N
TEAEs Leading To Study Drug Discontinuation by System Organ Class and Preferred Term	Y	Y
TEAEs Leading To Study Drug Discontinuation by System Organ Class and Preferred Term and CTCAE Grade	Y	N
TEAEs Leading to Death by System Organ Class and Preferred Term	Y	Y

Listings of all AEs and also all serious AEs will be produced.

A Listing will be produced for AEs with genetic information, actual drug received, and cycles on treatment.

8.4 Clinical Laboratory Evaluations

For hematology, chemistry, and coagulation, the observed values and changes from baseline will be summarized. Change from baseline will be calculated as (value at a treatment cycle – value at baseline). Laboratory results will be classified according to the NCI-CTCAE Version 4.03. Grades are assigned based solely on lab values and CTCAE requirements regarding related clinical signs or symptoms are not required.

Therefore, clinical assessment of the subjects could result in a different grade. Laboratory results not corresponding to CTCAE terms will not be graded. Thresholds are specified in Section 16.2. The number (%) of subjects with values that satisfy CTCAE criteria at any time during treatment will be summarized by test, grade, and visit. Each subject will be categorized based on their post-baseline CTCAE grade at each planned assessment time. Shift tables relative to the CTCAE Grade will be used to summarize the change from baseline to the maximum post-baseline CTCAE grade.

A table will summarize the shift in the absence/presence of protein, glucose, and blood in the urine.

Laboratory results will be summarized in standard international units.

Tables summarizing observed values and changes from baseline and shifts in CTCAE grade will be completed for study cohort. The number (%) of subjects with values that satisfy CTCAE criteria at any time during treatment will be provided for the treatment study cohort and integrated treatment group.

All laboratory test results (including urinalysis) will be presented in by-subject data listings. A list of abnormal laboratory values will also be produced where abnormal is defined as a value with CTCAE Grade 1 or higher. If a subject has at least one abnormal value for a specific analyte, all normal and abnormal values for that subject and analyte will be included in the listing.

Post baseline abnormal hepatic and renal results will be summarized by CTCAE Toxicity Grade among subjects with normal results prior to first dose, and a listing will be created to support this table.

8.4.1 Hematology

Blood samples for hematology will be analyzed for the collected time points. Hematology testing will include complete blood count (CBC) with differential and platelet counts.

8.4.2 Serum Chemistry

Blood samples for serum chemistry will be analyzed for the collected time points. Chemistry tests will include creatinine, creatinine clearance, sodium, potassium, calcium, magnesium, glucose, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin (TBIL), C-reactive protein (CRP), and blood urea. CTCAE grade for calcium will be based on corrected serum calcium, which will be calculated as follows:

Corrected serum calcium = serum calcium (mg/dL) + 0.8 *[(4 - serum albumin (g/dL)].

8.4.3 Coagulation

Blood samples for coagulation parameters will be collected will be analyzed for the collected time points. The coagulation parameters include international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

8.4.4 Urinalysis

Urine samples will be will be analyzed for the collected time points. A table will summarize the shift in the absence/presence of protein, glucose, and blood in the urine from baseline to day 1 of each cycle and the end of study visit.

8.5 ECG

12-Lead ECGs will be analyzed for the collected time points. ECG conduction times will include PR interval, QRS duration, QT and QTc interval using Fredericia's correction, and the heart rate. The observed values and changes from baseline will be summarized time points collected. Change from baseline will be calculated as (value at a treatment cycle – value at baseline). Frequencies and percentage of values meeting potentially clinically significant (PCS) criteria (Table 4) at any time will be presented. The denominator for percentages will be the number of patients who have a value at baseline and post-baseline.

Tables summarizing observed values and changes from baseline will be analyzed. The number (%) of subjects with values that satisfy PCS criteria at any time during treatment will be provided.

All summary tables will be provided for the Part 1 and 2 safety analysis set. All ECG data will be included in a listing.

Table 4: Potentially Clinically Significant Post-baseline ECG Conduction Times

Conduction Time	Unit	PCS Criteria
PR Interval	msec	Absolute value ≥ 200
QRS Duration	msec	Absolute value ≥ 100
QT Interval	msec	Absolute value ≥ 450
QTcF Interval	msec	Males: Absolute Value >= 450 Females: Absolute Value >= 470

Conduction Time	Unit	PCS Criteria
	msec msec	Increase from baseline 30 – 60 Increase from baseline > 60
Heart Rate	beats per minute	Absolute value ≤ 40 Absolute value ≥ 120

8.6 Vital Signs

For vital signs, the observed values and changes from baseline will be summarized by collected time points. Change from baseline will be calculated as (value at a treatment cycle – value at baseline). Frequencies and percentage of values meeting PCS criteria (Table 5) at any time post-baseline will be presented. The denominator for percentages will be the number of subjects who have a value at baseline and post-baseline.

Tables summarizing observed values and changes from baseline will be completed for the study cohorts. The number (%) of subjects with values that satisfy PCS criteria at any time during treatment will be provided for the study cohort and the integrated treatment group. PCS High criteria for BP are consistent with specific levels included in CTCAE criteria for Grade 1, 2, and 3 hypertension.

All vital sign data will be included in a by-subject data listing.

Table 5: Potentially Clinically Significant Post-Baseline Vital Signs

Vital Sign	Unit	PCS Low	PCS High
SBP	mmHg	Decrease from baseline ≥ 30 Absolute value <80 mmHg	Increase from baseline ≥ 30 Absolute value 121 – 139 Absolute value 140 – 159 Absolute value ≥ 160
DBP	mmHg	Decrease from baseline ≥ 20 mmHg Absolute value <60 mmHg	Increase from baseline ≥ 20 Absolute value 80 – 89

Vital Sign	Unit	PCS Low	PCS High
			Absolute value 90 – 99 Absolute value ≥ 100
Pulse	beats per minute	Absolute value ≤ 40	Absolute value ≥ 120
Respiratory Rate	breaths per minute	Absolute value < 12	Absolute value > 20
Weight	kg	≥ 7% decrease from Baseline	≥ 7% increase from Baseline

8.7 Immunogenicity

Blood samples for immunogenicity testing will be analyzed for the collected time points. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable binding and/or neutralizing anti-imalumab antibodies.

Summaries will be based upon all subjects from the safety population. The effect of immunogenicity on PK, PD, efficacy and safety will be evaluated, but such analyses, if applicable, will be summarized in a separate report.

9. EVALUATION OF PHARMACOKINETICS

A listing of PK blood sample collection times, derived sampling times, and imalumab concentrations will be provided.

Plasma concentrations of imalumab during Cycle 1 will be summarized by dose level, treatment group, and study day/measurement time interval using descriptive statistics (number of subjects [N], number of observations [n], mean, SD, coefficient of variation [CV%], median, minimum, and maximum). If n for a summary level is ≥3, all descriptive statistics will be presented; if n = 2, mean, median, minimum, and maximum will be presented and all other descriptive statistics will be reported as not determined (ND); if n = 1, the single available value will be presented for mean, median, minimum, and maximum, and all other descriptive statistics will be reported as ND. For the 10 mg/kg treatment groups, concentrations will be summarized separately by study part and for

both study parts combined. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics.

Subjects and/or data affected by protocol deviations or events that impact PK (such as incorrect dose, etc.) will be included in listings but excluded from descriptive statistics. A separate population PK analysis plan and corresponding report will be written to address the population PK analysis planned for this study.

10. EVALUATION OF QUALITY OF LIFE

10.1 Quality of Life Scoring

10.1.1 EORTC QLQ-C30 and QLQ-CR29

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) (Aaronson et. al., 1993) supplemented by the colorectal cancer module (QLQ-CR29) (Whistance et. al., 2009) are validated instruments and will be used to measure quality of life and assess symptoms and side effects of treatment and their impact on everyday life.

The QLQ-C30 is composed of 5 multi-item functional scales (physical, role, social, emotional and cognitive functioning), a global health status/QoL scale, and 9 symptom scales (fatigue, nausea/vomiting, pain, financial impact, appetite loss, diarrhea, constipation, sleep disturbance and dyspnea).

The colorectal cancer module (QLQ-CR29) incorporates functional scales to assess body image, anxiety, weight, and sexual interest. The QLQ-CR29 also includes symptom scales to assess urinary frequency, blood and mucus in stool, stool frequency, urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, flatulence, fecal incontinence, sore skin, embarrassment, stoma care problems, impotence, and dyspareunia.

Most items are answered on a 4-point scale (i.e., 1=Not at all, 2=A Little, 3=Quite a Bit, 4=Very Much) except the items contributing to the global health status/QoL, which have a 7-point scale (1=Very Poor to 7=Excellent). Raw scores (reported on eCRFs) will be transformed using a linear transformation to standardize the results so that scores for each functional and symptom scale range from 0 to 100.

The calculation for scoring these scales is the same in all cases (Fayers et. al., 2001)

1. Calculate the average of the items that contribute to the scale; this is the raw score.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Calculations for raw score and linear transformation are as follows:

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, where n is number of items in the scale, the procedure is as follows:

Raw score

RS (Raw Score) = $(I_1 + I_2 + I_3 + \ldots + In)$/n

Linear transformation

Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: S = {1 – (RS - 1)/range} x 100

Symptom scales / items: S = {(RS - 1)/range} x 100

Global health status / QoL: S = {(RS - 1)/range} x 100

Range is the difference between the maximum possible value of *RS* and the minimum possible value.

The raw score and linear transformed score will be calculated when at least 50% of the items from the scale have been answered. Otherwise, the score will be missing.

The structure of this questionnaire and scoring are presented in **Table 6** and **Table 7**.

Table 6: Scoring for QLQ-C30 version 3.0

Scale	Scale abbreviation	Number of items	Range	Item Number
Global health status / QoL				
Global health status/QoL	QL	2	6	29, 30
Functional scales				
Physical functioning	PF	5	3	1 to 5
Role functioning	RF	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18

Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhea	DI	1	3	17
Financial difficulties	FI	1	3	28

Table 7: Scoring for QLQ-CR29

Scale	Scale abbreviation	Number of items	Range	Item Number
Functional scales				
Body Image	BI	3	3	15-17
Anxiety	ANX	1	3	13
Weight	WEI	1	3	14
Sexual interest (men)	SEXM	1	3	26[a,c]
Sexual interest (women)	SEXW	1	3	28[a,c]
Symptom scales / items				
Urinary frequency	UF	2	3	1,2
Blood and mucus in stool	BMS	2	3	8,9
Stool frequency	SF	2	3	22,23[b]
Urinary incontinence	UI	1	3	3
Dysuria	DY	1	3	4
Abdominal pain	AP	1	3	5
Buttock pain	BP	1	3	6
Bloating	BF	1	3	7
Dry mouth	DM	1	3	10
Hair loss	HL	1	3	11
Taste	TA	1	3	12
Flatulence	FL	1	3	19[b]
Fecal incontinence	FI	1	3	20[b]
Sore skin	SS	1	3	21[b]
Embarrassment	EMB	1	3	24[b]
Stoma care problems	STO	1	3	25
Impotence	IMP	1	3	27[a]
Dyspareunia	DSY	1	3	29[a]

[a] Note that items 26 and 27 are for men only, and items 28 and 29 are for women only. Thus, these questions will be answered only by a subset of patients.
[b] When scoring scales or single items that include questions 19 to 24, use the answer to question 18: 'Do you have a soma bag (colostomy/ileostomy)? Yes/No to ensure that answers are taken from the relevant box of questions
[c] In order for the two sexual interest scales to be interpreted as functional scales (i.e. a higher score is better), they should be scored according to the symptom scale algorithm.

10.1.2 EQ-5D-5L

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no

problems, slight problems, moderate problems, severe problems, and unable to perform the activity. There will be no imputation of missing data. In addition, the EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 0='the best health you can imagine' and 100='the worst health you can imagine'.

10.2 Analysis of QoL Data

For each QLQ-C30 and QLQ-CR29, the summary statistics of absolute scores and changes from baseline will be calculated for the linear transformed score for Global Health status, functional and symptom scale for the Safety Analysis Set.

For Part 2, the study drug and SoC is compared by a 2-sided Wilcoxon rank sum test with the t-Approximation at an alpha of 0.05.

For each of the 5 dimensions of the EQ-5D, tables will be provided to summarize the frequency and percentage of subjects with no, slight, moderate, and severe problems with or were unable to perform each dimension at baseline and end of study. In addition, the shift in the levels of perceived problems at baseline to the levels of perceived response at end of study will be summarized. The EQ VAS and change from baseline will be summarized by study cohort.

All summary tables will be provided for the study cohorts. Data for all subjects will be included in listings.

11. EVALUATION OF EXPLORATORY OUTCOME MEASURES

11.1 Evaluation of Pharmacodynamics

A listing of blood sample collection times, derived sampling times, and observed, change from baseline and percent change from baseline values will be provided for total MIF and oxMIF data. Baseline for total MIF and oxMIF will be the Day 1 measurement at -2 to 0 hours prior to start of infusion.

Total MIF and oxMIF data during Cycle 1 will be summarized by dose level and treatment group using descriptive statistics (number of patients [N], number of observations [n], mean, SD, median, minimum, and maximum). If n for a summary level is ≥ 3, all descriptive statistics will be presented; if n = 2, mean, median, minimum, and maximum will be presented and all other descriptive statistics will be reported as not determined (ND); if n = 1, the single available value will be presented for mean, median, minimum, and maximum, and all other descriptive statistics will be reported as ND. For

the 10 mg/kg treatment groups, data will be summarized separately by study part and for both study parts combined. Total MIF and oxMIF that are below the limit of quantitation (BLQ) will be set to 1/2 the lower limit of quantitation (LLOQ) for the calculation of change from baseline values, and for the computation of descriptive statistics for observed values.

11.2 Exploratory Quality of Life Outcome Measures

Analyses of EORTC QLQ-CR29 symptom and functional scales as well as the EQ-5D-5L dimensions are described in Sections 10.1 and 10.2.

11.3 Genetic Biomarkers

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 objectives are exploratory and subject-approval for blood/urine collection is optional, analyses will be data driven. Data summaries will be developed and prepared based on an assessment of the available data at the time of the primary analysis.

12. ANALYSIS SOFTWARE

All data processing, summarization and analyses will utilize SAS® software package, Version 9.4. If the use of other software is warranted, the final clinical study report will detail what software was used.

13. GUIDANCE DOCUMENTS

Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

E3 Structure and Content of Clinical Study Reports

E9 Statistical Principles for Clinical Trials

14. REFERENCES

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Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *EORTC QLQ-C30 Scoring Manual (3rd edition)*. Brussels: EORTC, 2001. ISBN: 2-9300 64-22-6.

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15. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2016 OCT 06	New Document

16. APPENDICES

16.1 Schedule of Study Procedures and Assessments

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 / **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								
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

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 / 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								
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]

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 / **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								
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	
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.

[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 (± 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.

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[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 of the protocol. ***Cycle 1 only:*** Blood samples will be collected predose and postdose on Day 1, on either Day 2 (24 ± 4 h post first dose) OR Day 4 (72 ± 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.

16.2 CTC grades for laboratory values

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematology				
Activated partial thromboplastin time prolonged (aPTT)	>ULN - 1.5 x ULN	>1.5 x ULN - 2.5 x ULN	> 2.5 x ULN	
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN	
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L;	
INR increased*	>ULN - 1.5 x ULN;	>1.5 x ULN - 2.5 xULN;	>2.5 x ULN;	
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Lymphocyte count increased		>4000/mm3 - 20,000/mm3	>20,000/mm3	
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9/L	<25,000/mm3; <25.0 x 10e9 /L
White blood cell decreased (WBC)	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Clinical Chemistry				
Albumin decreased (Hypoalbuminemia)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alanine aminotransferase increased (ALT or SGPT)	>ULN - 3.0 x ULN	>3.0 x ULN - 5.0 xULN;	>5.0 x ULN - 20.0 xULN;	>20.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5.0 x ULN	>5.0 x ULN - 20.0 x ULN	>20.0 x ULN
Amylase increased	>ULN - 1.5 x ULN	>1.5 x ULN - 2.0 x ULN	>2.0 x ULN - 5.0 x ULN	>5.0 x ULN
Aspartate aminotransferase increased (AST or SGOT)	>ULN - 3.0 x ULN	>3.0 x ULN - 5.0 x ULN;	>5.0 x ULN - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 x ULN - 3.0 x ULN	>3.0 x ULN - 10.0 x ULN	>10.0 x ULN
Calcium high[2)] (Hypercalcemia)	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L;	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L;	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L;	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L;
Calcium low[2)] (Hypocalcaemia)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L;	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;
Creatinine increased	> baseline - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 x baseline - 3.0 x baseline; >1.5 x ULN - 3.0 x ULN	>3.0 x baseline; > 3.0 x ULN - 6.0 x ULN	>6.0 x ULN
Glucose decreased (Hypoglycemia)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L;
Glucose increased (Hyperglycemia)	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	Fasting glucose value >250 - 500 mg/dL; Fasting glucose value >13.9 - 27.8 mmol/L;	Fasting glucose value >500 mg/dL; Fasting glucose value >27.8 mmol/L;
Magnesium high (Hypomagnesaemia)	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L		>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L;

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Magnesium low (Hypomagnesaemia)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L;
Potassium high (Hyperkalemia)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L;	>7.0 mmol/L;
Potassium low* (Hypokalemia)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L;	<3.0 - 2.5 mmol/L;	<2.5 mmol/L;
Sodium high (Hypernatremia)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L;
Sodium low (Hyponatremia)	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L;
Uric Acid high* (Hyperuricemia)	>ULN - 10 mg/dL (0.59 mmol/L)	-	>ULN - 10 mg/dL (0.59 mmol/L)	>10 mg/dL; >0.59 mmol/L;

[1)] Because many institutions have differences for normal ranges of metabolic, laboratory, and hematology values, the CTCAE often uses the terms ULN and LLN in lieu of actual numerical values. In some cases, an institution's LLN might be beyond the range specified for a Grade 1. In this case, the institutional limits of normal should take precedence over the CTCAE values. For example, if an institution's LLN of lymphocytes is 500/mm^3, a lymphocyte count of 501 at that institution would be translated to a CTCAE Grade 0; a lymphocyte count of 499 would be translated to a CTCAE Grade 3. Because local laboratory values trump CTCAE v4.03's ranges, some Grade 1 and Grade 2 AEs will not exist for a local lab.

[2)] Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4]