Official Title of Study:

A Randomized, Open-label, Phase II Clinical Trial of Relatlimab (anti-LAG-3) and Nivolumab in Combination with Chemotherapy Versus Nivolumab in Combination with Chemotherapy as First-Line Treatment in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma

NCT Number: NCT03662659

Document Date (Date in which document was last revised): June 24, 2019

Protocol Number: CA224060
IND Number: 137615
EUDRACT Number: 2018-001069-18
Date: 02-Apr-2018
Revised Date: 24-Jun-2019

Clinical Protocol CA224060

A Randomized, Open-label, Phase II Clinical Trial of Relatlimab (anti-LAG-3) and Nivolumab in Combination with Chemotherapy Versus Nivolumab in Combination with Chemotherapy as First-Line Treatment in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma

Short Title:

An Open Label Study of Relatlimab and Nivolumab with Chemotherapy Versus Nivolumab with Chemotherapy in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma

Revised Protocol 03
Incorporates Administrative Letters: 01 and 02

[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	24-Jun-2019	Revised to update with current program requirements, updated company standards, and to provide additional clarifications throughout
Administrative Letter 02	11-Dec-2018	Corrected an error in the Document History page of Revised Protocol 02
Administrative Letter 01	30-Nov-2018	Study title was updated to: An Open Label Study of Relatlimab and Nivolumab with Chemotherapy Versus Nivolumab with Chemotherapy in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma
Revised Protocol 02	16-Nov-2018	[redacted] Revised text reflecting addition of Data Monitoring Committee Modified language requiring pathology report to accompany FFPE tissue block or unstained tumor tissue section for biomarker evaluation; pathology report is optional [redacted] Revised exclusion for participants who received live or attenuated vaccines within 30 days of treatment Added prohibition of any live/attenuated vaccine during treatment up to 100 days post treatment Removed exclusion of recombinant human erythropoietin within 3 weeks of first study drug administration Added text regarding treatment access rules Removed a pre-screening consent option [redacted] Updated Appendix 3 (AEs and SAEs) Updated Appendix 8 (added myocarditis management algorithm)
Revised Protocol 01	29-Jun-2018	Modified PD-L1 stratification levels for statistical analyses Additional exclusion criterion added [redacted] Revised discontinuation from study treatment to include consideration of abnormal liver test results and procedures to follow in case of pregnancy Revised time period and frequency for collecting AE and SAE information [redacted] Updated appendix for WOCBP Updated CTCAE to version 5 Minor formatting and typographical corrections
Original Protocol	02-Apr-2018	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 03:

This protocol revision serves to update the protocol with updated program requirements, updated company standards, as well as providing additional clarifications throughout.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Study Population; Synopsis, Key Inclusion Criteria; Synopsis, Objectives and Endpoints; Synopsis, Overall Design; 3, Introduction; [redacted] 3.2.1, Research Hypothesis; Table 4-1: Objectives and Endpoints; 5.1, Overall Design; [redacted] 6.1, Inclusion Criteria 2), a) and b)	Updated study population description.	Clarified the specific population.
Synopsis, Key Inclusion Criteria	Updated several criteria and added a criterion for left ventricular ejection fraction.	Clarified for program updates and company requirements.
Synopsis, Study Treatment	Updated FOLFOX treatment description.	Clarified treatment cycles.
Table 2-1: Screening Assessments - All Participants (CA224060)	Add clarification of timing to Informed Consent.	Clarified timing.
Table 2-2: On-treatment Assessments - Participants Assigned to Investigator's Choice XELOX or SOX (CA224060); Table 2-3: On-treatment Assessments - Participants Assigned to Investigator's Choice FOLFOX (CA224060)	Add clarification of timing to Troponin assessment.	Clarified timing.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.1, Screening Phase	Updated timing of Informed Consent and clarified tumor tissue sample specifications.	Clarified timing and requirements.
5.1.5, Data Monitoring Committee	Add language regarding adjudication.	Updated to company standards.
[redacted]		
6.1, Inclusion Criteria 2), d)	Removed criteria for evaluable disease.	Removes ambiguity.
6.1, Inclusion Criteria 2), f)	Updated tumor tissue requirements.	Clarification for sites.
6.1, Inclusion Criteria 3), a)	Updated to add age of majority.	Aligns with company standards.
6.2, Exclusion Criteria 1), i), ix)	Added criteria for left ventricular ejection fraction assessment.	Provides additional safety information.
6.2, Exclusion Criteria 3), f)	Updated AST/ALT requirements.	Updated for clarification for sites.
6.2, Exclusion Criteria 3), h)	Updated troponin assessment.	Updated for clarification for sites.
6.4, Screen Failures	Updated reporting requirements.	Aligns with company standards.
7, Treatment	Added additional text describing treatments administered.	Aligns with company standards.
7.1.1, BMS-986213 or Nivolumab Dosing	Added text noting dosing visits should not be skipped, only delayed.	Clarification to align with program standards.
7.1.2, Dose Schedule for BMS-986213 or Nivolumab Plus XELOX	Updated premedications language.	Clarification for sites to better address patient safety.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.1.3, Dose Schedule for BMS-986213 or Nivolumab Plus FOLFOX	Updated FOLFOX treatment description; updated premedications language.	Clarified treatment cycles; Clarification for sites to better address patient safety.
7.1.4, Dose Schedule for BMS-986213 or Nivolumab Plus SOX	Updated premedications language.	Clarification for sites to better address patient safety.
7.2, Method of Treatment Assignment	Added language describing participant enrollment; Moved randomization language to blinding section.	Adds clarification for sites as well as aligns with company standards.
7.3.6, Criteria to Resume BMS-986213 or Nivolumab Treatment	Updated AST/ALT to AST and/or ALT.	Clarification for sites.
7.3.7, Criteria for BMS-986213 or Nivolumab Discontinuation	Added text requiring periodic study visits.	Aligns with program standards.
7.8, Blinding	Added new section to describe randomization and monitoring procedures.	Aligns with company standards.
9.1.1, Imaging Assessment for the Study	Added text to address additional imaging assessments.	Aligns with company standards.
9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Updated collection start from randomization and removed from treatment assignment.	Clarification for sites.
9.2.5, Pregnancy	Added additional language regarding pregnancy discontinuations; Added text regarding fetal toxicity.	[redacted] Aligns with company standards.
Table 9.4.4-1: Laboratory Assessment Panels	Updated pregnancy test and FSH requirements.	Aligns with company standards.
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 2, Study Governance Considerations	Revised text throughout.	Aligns with company standards.
Global	Fixed minor typos.	Minimal, therefore not summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title:

A Randomized, Open-label, Phase II Clinical Trial of Relatlimab (anti-LAG-3) and Nivolumab in Combination with Chemotherapy Versus Nivolumab in Combination with Chemotherapy as First-Line Treatment in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma

Short Title:

An Open Label Study of Relatlimab and Nivolumab with Chemotherapy Versus Nivolumab with Chemotherapy in Patients with Gastric or Gastroesophageal Junction Adenocarcinoma

Study Phase: 2

[redacted]

Study Population:

The study population includes adult participants with unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma, independent of LAG-3 expression, with no prior systemic treatment.

Key Inclusion Criteria:

- Males and females, ≥18 years of age or age of majority
- Eastern Cooperative Oncology Group performance status score of 0 or 1
  - Tumor tissue must be provided for analysis prior to randomization. In order to be randomized, the participant's tumor associated immune cells must have an evaluable LAG-3 status (≥1% or <1%; no indeterminate allowed) and must have an evaluable PD-L1 status (CPS < 1 or indeterminate, CPS ≥ 1 to <5, CPS ≥ 5).
- Participants must have histologically- or cytologically-confirmed diagnosis of unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.
- Participants must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma
- Participants must have at least one measurable lesion by computed tomography or magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria; radiographic tumor assessment should be performed within 28 days prior to randomization.

Key Exclusion Criteria:

- Participants with HER2 positive status [IHC3+ or FISH positive (HER2:CEP17 ratio > 2) or IHC2+/FISH+]
- Participants with known untreated central nervous system (CNS) metastases
- Participants with ascites which cannot be controlled with appropriate interventions
- Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
  - Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent
  - Uncontrolled angina within the 3 months prior to consent
  - Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes or poorly controlled atrial fibrillation)
  - QTc prolongation > 480 msec
  - History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled deep venous thrombosis, etc)
  - Cardiovascular disease-related requirement for daily supplemental oxygen
  - History of 2 or more MIs OR 2 or more coronary revascularization procedures
  - Participants with history of myocarditis, regardless of etiology

  - Left ventricular ejection fraction (LVEF) < 50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition (MUGA) scan (TTE is preferred test) within 6 months prior to date of first study drug administration.
- Troponin T (TnT) or I (TnI) > 2 × institutional upper limit of normal (ULN). Participants with TnT or TnI levels between > 1 to 2 × ULN will be allowed to enroll if a repeat assessment remains within ULN or patient has no cardiac symptoms and participant undergoes a cardiac imaging evaluation found to have no significant myocardial disease or dysfunction. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To compare objective response rate (ORR) of BMS-986213 in combination with chemotherapy, with ORR of nivolumab in combination with chemotherapy, by BICR, in randomized participants with untreated, unresectable, and either locally advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma.	• ORR in participants who are LAG-3 positive. ORR is defined as the number of participants with a best overall response (BOR) of CR or PR divided by the number of randomized participants in each arm. BOR is defined as the best response designation as determined by the blinded independent central review (BICR), recorded between the date of randomization and the date of objectively documented progression (per Response Evaluation Criteria in Solid Tumors [RECIST 1.1]), death due to any cause, or the date of subsequent anti-cancer therapy, whichever occurs first.
Secondary	
• To assess the overall safety and tolerability of BMS-986213 in combination with chemotherapy vs. nivolumab in combination with chemotherapy in treated participants with advanced or metastatic GC or GEJ cancer.	• The incidence of adverse events (AEs), serious AEs (SAEs), AE leading to discontinuation, deaths, and laboratory abnormalities in each arm.
• To compare objective response rate (ORR) of BMS-986213 in combination with chemotherapy, with ORR of nivolumab in combination with chemotherapy, as assessed by investigator, in randomized participants with untreated, unresectable, and either locally advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma.	• ORR is defined as above, as the number of participants with a BOR of CR or PR as assessed by the investigator using RECIST 1.1, divided by the number of randomized participants in each Treatment Arm,
• To compare ORR by BICR and by investigator of BMS-986213 in combination with chemotherapy with ORR of nivolumab in combination with chemotherapy in randomized participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma, and in the overall population (arcoss LAG-3 negative and positive groups).	• ORR in the LAG-3 negative group or in the overall population is defined as above, as the number of participants in each population with a BOR of CR or PR divided by the number of randomized participants in each Treatment Arm, for that population.
• To estimate Duration of Response (DOR) of BMS-986213 in combination with chemotherapy and DOR of nivolumab in combination with	• DOR (based on BICR and investigator) is defined as the time between the date of first documented response (CR or PR) and the date of the first disease

Objective	Endpoint
chemotherapy in randomized participants with advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma, by BICR and by the investigator.	progression, per RECIST 1.1, death due to any cause, or the date of subsequent anti-cancer therapy whichever occurs first. .
• To estimate DOR of BMS-986213 in combination with chemotherapy and DOR of nivolumab in combination with chemotherapy in randomized participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma, and in the overall population, by BICR and by the investigator	• DOR in participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma and for participants in the overall population (across the LAG-3 groups) is defined as above.
• To assess the difference in the overall survival (OS) of BMS-986213 in combination with chemotherapy and OS of Nivolumab in combination with chemotherapy in randomized participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma separately in the LAG-3 positive and LAG-3 negative groups and overall.	• Overall survival. OS is defined as the time between the date of randomization and the date of death. For those without documentation of death, OS will be censored on the last date the participant was known to be alive.
• To assess the difference in the progression-free survival (PFS) of BMS-986213 in combination with chemotherapy and PFS of nivolumab in combination with chemotherapy as assessed by BICR and investigator in randomized participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma separately in the LAG-3 positive and LAG-3 negative groups and overall.	• PFS is defined as the time between the date of randomization and the date of the first documented PD per BICR or investigator or death due to any cause. Participants who die without a reported prior PD per BICR or investigator (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Those who did not have documented PD per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of subsequent anti-cancer therapy) will be censored at the randomization date. Those who started any subsequent anti-cancer therapy without a prior reported PD will be censored at the last tumor assessment prior to or on the initiation of the subsequent anti-cancer therapy. Participants receiving treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

Overall Design:

- This is a Phase 2, randomized, open-label, two-arm study of BMS-986213 (fixed-dose combination [FDC] relatlimab/nivolumab) or nivolumab in combination with investigator's choice chemotherapy as first-line treatment in participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma.
- Depending on the assigned treatment arm, the participant will receive BMS-986213 in combination with investigator's choice chemotherapy or nivolumab in combination with investigator's choice chemotherapy.
- One cycle of treatment is defined as 6 weeks.

Number of Participants:

It is expected that approximately 420 participants will need to be enrolled in order to randomize 250 participants; 40% of screened participants are expected to screen fail.

Approximately 250 participants are planned to be randomized to one of 2 treatment arms:

1) BMS-986213 in combination with investigator's choice chemotherapy
2) Nivolumab in combination with investigator's choice chemotherapy

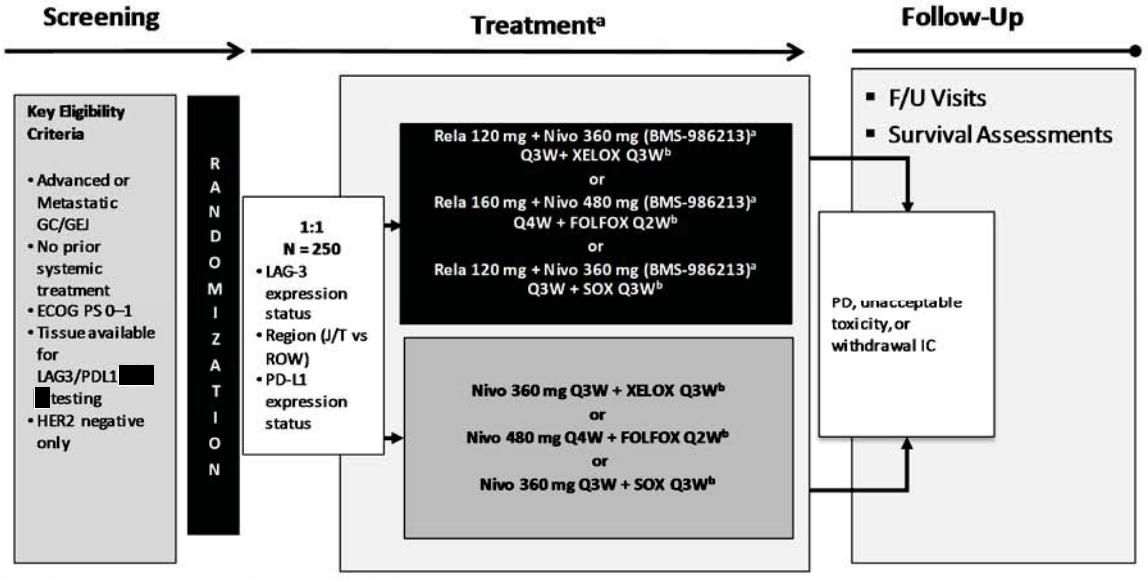
The sample size is calculated in order to compare the ORR between participants with LAG-3 positive expression randomized to receive BMS-986213 + Investigator's choice Chemotherapy vs Nivolumab + Investigator's choice Chemotherapy. [redacted]

Study Treatments:

Study Treatments for CA224060		
Medication	**Potency**	**Investigational Product (IP)/Non-IP**
BMS-986213 (Relatlimab 80 mg/ Nivolumab 240 mg)	16 mg/mL	IP
Nivolumab (BMS-936558-01) Solution for Injection	10 mg/mL	IP
Oxaliplatin Concentrate for Solution for Infusion	5 mg/mL	IP
Capecitabine Tablet	150 mg and 500 mg tablets	IP
Fluorouracil Solution for Injection	50 mg/ mL	IP
Leucovorin (folinic acid) Solution for Injection	50 mg/mL	IP
S-1 tegafur/gimeracil/oteracil Capsule	20 mg/5.8 mg/15.8 mg	IP

Study Treatments for CA224060		
Medication	**Potency**	**Investigational Product (IP)/Non-IP**
S-1 tegafur/gimeracil/oteracil Capsule	15 mg/4.35 mg/11.8 mg	IP

The study design schematic is presented below.



[a] Fixed dose combination of relatlimab [anti-LAG-3] plus nivolumab

[b] Investigator Choice Chemo:

1. **XELOX:** oxaliplatin 130 mg/m² administered IV on Day 1 of each treatment cycle and capecitabine 1000 mg/m² administered orally twice daily on Days 1 to 14 of each treatment cycle, every 3 weeks
2. **FOLFOX:** oxaliplatin 85 mg/m², leucovorin 400 mg/m² and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks.
3. **SOX:** oxaliplatin 130 mg/m² administered IV on Day 1 of each treatment cycle and oral S-1 twice daily on Day 1 to 14 of each treatment cycle, every 3 weeks. S-1 dose was calculated according to body surface area (BSA, mg/m²/dose): BSA <1.25 m², 40 mg/dose; ≥1.25 and <1.5 m², 50 mg/dose; ≥1.5 m², 60mg/dose.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; F/U = follow-ip; GC = gastric cancer; GEJ = gastroesophageal junction; IC = informed consent; J = Japan; LAG-3 = lymphocyte activation gene 3; PD-L1 = programmed death-ligand 1; PS = performance status; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; T = Taiwan; ROW = Rest of World

During the treatment phase, participants will receive BMS-986213 or nivolumab in combination with investigator's choice of chemotherapy (XELOX, FOLFOX, or SOX):

- Participants assigned to XELOX will receive BMS-986213 (relatlimab 120 mg/nivolumab 360 mg) or nivolumab 360 mg, administered intravenously (IV) over 60 minutes or 30 minutes, respectively, and oxaliplatin 130 mg/m^2 administered IV on Days 1 and 22 of each treatment

cycle every 6 weeks, and capecitabine 1000 mg/m^2 administered orally twice daily (AM and PM dosing) on Days 1 to 14 and Days 22 to 35 of each treatment cycle every 6 weeks.

- Participants assigned to FOLFOX will receive BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) or nivolumab 480 mg administered IV over 60 minutes or 30 minutes, respectively, on Days 1 and 29 of every odd numbered 6-week treatment Cycle (Cycle 1, 3, 5, etc) and Day 15 of every even numbered 6-week treatment Cycle (Cycle 2, 4, 6, etc). Oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 will be administered IV on Days 1, 15, and 29 of each treatment cycle every 6 weeks, and fluorouracil 1200 mg/m2 IV continuous infusion over 24 hours daily (or per local standard) on Days 1 & 2, 15 & 16, and 29 & 30 of each treatment cycle every 6 weeks. As a consequence of this dosing regimen, FOLFOX will be administered alone, without immunotherapy, on Day 15 of each odd numbered 6-week treatment cycle and Days 1 and 29 of each even numbered 6-week treatment cycle.
- Participants assigned to SOX will receive BMS-986213 (relatlimab 120 mg/nivolumab 360 mg), or nivolumab 360 mg, administered IV over 60 minutes or 30 minutes, respectively, and oxaliplatin 130 mg/m^2 administered IV on Days 1 and 22 of each treatment cycle every 6 weeks, and oral S-1 twice daily on Days 1 to 14 and Days 22 to 35 of each treatment cycle, every 6 weeks. S-1 (tegafur/gimeracil/oteracil) dose as calculated according to body surface area (BSA, mg/m^2/dose): BSA <1.25 m^2, 40 mg/dose; ≥ 1.25 and <1.5 m^2, 50 mg/dose; ≥ 1.5 m^2, 60 mg/dose

No dose reductions of BMS-986213 or nivolumab are permitted, only dose delays are permitted. Dose modifications for Investigator's choice chemotherapy are permitted. Treatment may be discontinued due to unacceptable toxicity, withdrawal of consent, disease progression, or termination of the study, whichever occurs first. Participants treated with BMS-986213 or nivolumab in combination with chemotherapy will be permitted to continue their treatment beyond initial RECIST 1.1-defined PD, assessed by the investigator, as long as they meet the appropriate criteria and the investigator believes continuing treatment is in the patient's best interests.

Data Monitoring Committee:

A Data Monitoring Committee has been included and is detailed in Section 5.1.5.

[redacted]

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Assessments - All Participants (CA224060)

Procedure	Screening Visit	Notes All windows are based on calendar days.
Eligibility Assessments		
Informed Consent	X	Informed consent must occur prior to any screening procedure and within 28 days of randomization. Contact interactive response technology (IRT) to obtain study subject number. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new subject number from IRT.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization.
Medical History	X	Including concomitant medications and prior cancer therapy.
Tumor Tissue Samples	X	Recent sample or archival. Sufficient tumor tissue (either a formalin-fixed, paraffin-embedded [FFPE] tissue block or minimum 20 positively charged slides*) must be available within 3 months prior to randomization, with no intervening systemic therapy, and sent to a central laboratory for biomarker analysis. Tissue must be a core needle biopsy, excisional biopsy, or incisional biopsy. Fine needle biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. * If, despite best efforts, a minimum 20 slides are not obtainable, discuss with Sponsor. In order to be randomized, the participant's tumor-associated immune cells must have an evaluable lymphocyte activation gene 3 (LAG-3) status (≥ 1% or < 1%; no indeterminate allowed) and must have a PD-L1 status (combined positive score [CPS] < 1 or indeterminate, CPS ≥ 1 to < 5, CPS ≥ 5). [redacted]
[redacted]		
Safety Assessments		
Physical Examination	X	Within 14 days prior to randomization.

Table 2-1: Screening Assessments - All Participants (CA224060)

Procedure	Screening Visit	Notes All windows are based on calendar days.
Physical Measurements	X	Include height, weight, and body surface area (BSA). Within 14 days prior to randomization.
Performance Status (ECOG)	X	Within 14 days prior to randomization. See protocol Appendix 6.
Vital Signs	X	Obtain vital signs at the screening visit and within 72 hours prior to first dose. Including blood pressure (BP), heart rate, and temperature.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Within 28 days prior to randomization.
Serious Adverse Events Assessment	X	Serious Adverse Event collection from time of consent.
Laboratory Tests	X	Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1 within 14 days prior to randomization. Serology as outlined in Table 9.4.4-1 within 28 days prior to randomization. For HIV: testing at sites where locally mandated, see Appendix 7.
Troponin	X	Within 14 days prior to randomization.
Echocardiogram	X	Left ventricular ejection fraction (LVEF) assessment with documented LVEF ≥ 50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition (MUGA) scan (TTE is preferred test) within 6 months prior to date of first study drug administration.
Electrocardiogram (ECG)	X	At rest. Within 14 days prior to randomization.
Pregnancy Test (WOCBP only)	X	Serum - (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment.
Follicle-stimulating Hormone	X	If needed to document postmenopausal status as defined in Table 9.4.4-1.

Table 2-1: Screening Assessments - All Participants (CA224060)

Procedure	Screening Visit	Notes All windows are based on calendar days.
Efficacy Assessments		
Body Imaging	X	See Section 9.1.1. Must be performed within 28 days prior to randomization.
Brain Imaging	X	See Section 9.1.1. magnetic resonance imaging (MRI) of the brain without and with contrast is required if participant is symptomatic or has history of brain metastasis and has not had brain imaging within 28 days prior to anticipated first study drug administration. Computed tomography (CT) of the brain (without and with contrast) can be performed if MRI is contraindicated.
Interactive Response Technology (IRT)		
Contact IRT	X	The IRT must be contacted for subject number assignment at the time informed consent is obtained.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; WOCBP = women of childbearing potential.

Table 2-2: On-treatment Assessments - Participants Assigned to Investigator's Choice XELOX or SOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
Safety Assessments			
Targeted Physical Examination	X	See note	To be performed within 72 hours prior to dosing on Days 1 and 22 of each cycle.
Vital Signs	X	See note	Including BP, heart rate, and temperature to be performed within 72 hours prior to dosing on Days 1 and 22 of each cycle.
Weight and ECOG Performance Status	X	See note	To be performed within 72 hours prior to dosing on Days 1 and 22 of each cycle. See protocol Appendix 6 for ECOG Performance Status scale.
Adverse Event Assessment	Continuously		Assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
Serious Adverse Event Assessment	Continuously		Assessed using NCI CTCAE v5.
Review of Concomitant Medications	Continuously		
Laboratory Tests	X	See note	To be performed within 72 hours prior to dosing on Days 1 and 22 of each cycle. Includes Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1. All labs should be checked prior to dosing.
Troponin	See note	See note	Q2W or Q3W monitoring (depending on selected chemotherapy regimen) for the first 12 weeks. For immunotherapy dosing visits, test should be performed and evaluated within 72 hours prior to immunotherapy dosing. Note: Symptom-based troponin testing may be performed as required.
Pregnancy Test (WOCBP only)	X	See note	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose of study treatment and then every 4

Table 2-2: On-treatment Assessments - Participants Assigned to Investigator's Choice XELOX or SOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
			weeks (± 7 days) regardless of dosing schedule. If collected with a dosing visit, then obtain within 24 hours prior to administration of study drug. Home pregnancy test that meets the minimum sensitivity requirements can be used as necessary.
ECG	See note	See note	Cycle 1: Performed within 72 hours prior to dosing on Day 1 and Day 22. Cycles 2 to 4: Performed within 72 hours prior to dosing on Day 1. Cycle 5 and Beyond: Performed within 72 hours prior to dosing every 12 weeks starting with C5D1.
[redacted]			
Efficacy Assessments			
Body Imaging	See Note		See Section 9.1.1. Tumor assessments should occur every 6 weeks (± 7 days) starting from randomization up to and including Week 48, then every 12 weeks (± 7 days) regardless of treatment schedule until BICR-confirmed disease

Table 2-2: On-treatment Assessments - Participants Assigned to Investigator's Choice XELOX or SOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
			progression (PD) or the participant withdraws consent, whichever comes first. Participants who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent. Use same imaging method as was used at screening/baseline.
Brain Imaging	See note		See Section 9.1.1. Participants with a history of brain metastases or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks), or sooner if clinically indicated.
[redacted]			
Study Treatment			
Randomization	X		Contact IRT for randomization.

Table 2-2: On-treatment Assessments - Participants Assigned to Investigator's Choice XELOX or SOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
BMS-986213 or Nivolumab	X	See note	First dose of BMS-986213 or nivolumab and chemotherapy (XELOX or SOX) should be administered within 72 hours after randomization. **BMS-986213 or nivolumab should be administered on the same day as the chemotherapy, unless there is a dose delay or treatment is discontinued.** BMS-986213 or nivolumab must be administered within 3 days before or after the scheduled date. BMS-986213 should be administered in a single IV bag over 60 minutes. Nivolumab should be administered over 30 minutes.
XELOX or SOX and Dispense Drug Diary	X	See note	First dose to be administered within 72 hours after randomization. • XELOX dose schedule: see Table 7.1.2-1. Subsequent XELOX doses may be administered within dosing windows per package insert or local standard. • SOX dose schedule: see Table 7.1.4-1. Subsequent SOX doses may be administered within dosing windows per package insert or local standard. Review Drug Diary during each visit for compliance of twice daily administration of Capecitabine or S-1. Collect Drug Diary at the completion of each cycle.

Abbreviations: BICR = blinded independent central review; BP = blood pressure; C = cycle; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] HCG = human chorionic gonadotropin; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MRI = magnetic resonance imaging; [redacted] SOX = S1 and oxaliplatin; WOCBP = women of childbearing potential; XELOX = capecitabine and oxaliplatin.

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs, except for body imaging, [redacted] and pregnancy testing.

Table 2-3: On-treatment Assessments - Participants Assigned to Investigator's Choice FOLFOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
Safety Assessments			
Targeted Physical Examination	X	See note	To be performed within 72 hours prior to dosing on Days 1, 15, and 29 of each cycle.
Vital Signs	X	See note	Including BP, heart rate, and temperature to be performed within 72 hours prior to dosing on Days 1, 15, and 29.
Weight and ECOG Performance Status	X	See note	To be performed within 72 hours prior to dosing on Days 1, 15, and 29. See protocol Appendix 6 for ECOG Performance Status scale.
Adverse Event Assessment	Continuously		Assessed using NCI CTCAE v5
SAE Assessment	Continuously		Assessed using NCI CTCAE v5
Review of Concomitant Medications	Continuously		
Laboratory Tests	X	See note	To be performed within 72 hours prior to dosing on Days 1, 15, and 29. Includes Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1. All labs should be checked prior to dosing.
Troponin	See note	See note	Q2W or Q3W monitoring (depending on selected chemotherapy regimen) for the first 12 weeks. For immunotherapy dosing visits, test should be performed and evaluated within 72 hours prior to immunotherapy dosing. Note: Symptom-based troponin testing may be performed as required.

Table 2-3: On-treatment Assessments - Participants Assigned to Investigator's Choice FOLFOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
Pregnancy Test (WOCBP only)	X	See Note	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose of study treatment and then every 4 weeks (± 7 days) regardless of dosing schedule. If collected with a dosing visit, then obtain within 24 hours prior to administration of study drug. Home pregnancy test that meets the minimum sensitivity requirements can be used as necessary.
ECG	See Note	See Note	Cycle 1: Performed within 72 hours prior to dosing on Days 1 and 15 Cycles 2-4: Performed within 72 hours prior to dosing on Day 1. Cycle 5 and Beyond: Performed within 72 hours prior to dosing every 12 weeks starting with C5D1
[redacted]			
Efficacy Assessments			
Body imaging	See Note		See Section 9.1.1. Tumor assessments should occur every 6 weeks (± 7 days) starting from randomization up to and including Week 48, then every 12 weeks (± 7 days) regardless

Table 2-3: On-treatment Assessments - Participants Assigned to Investigator's Choice FOLFOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
			of treatment schedule until BICR-confirmed PD or the participant withdraws consent, whichever comes first. Participants who discontinue study treatment for reasons other than PD will continue to have tumor assessments until their disease progresses or they withdraw consent. Use same imaging method as was used at screening/baseline
Brain Imaging	See Note		See Section 9.1.1. Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks), or sooner if clinically indicated
[redacted]			
Study Treatment			
Randomization	X		Contact IRT for randomization
BMS-986213, or Nivolumab	X	See Note	First dose of BMS-986213 or nivolumab and FOLFOX should be administered within 72 hours after randomization**. BMS-986213 or nivolumab should be administered every 4-weeks on the same day as FOLFOX, unless there is a dose delay or treatment is discontinued.** BMS-986213 or nivolumab may be administered within 3 days before or after the scheduled date if necessary. BMS-986213 should be administered in a single IV bag over 60 minutes. Nivolumab should be administered over 30 minutes.

Table 2-3: On-treatment Assessments - Participants Assigned to Investigator's Choice FOLFOX (CA224060)

Procedure[a]	Cycle 1 Day 1 (Cycle = 6 weeks)	Other Time Points Relative to Dosing Schedule	Notes
FOLFOX	X	See Note	First dose to be administered within 72 hours after randomization. FOLFOX dose schedule: see Table 7.1.3-1. Subsequent FOLFOX doses may be administered within dosing windows per package insert or local standard.

Abbreviations: BP = blood pressure; C = cycle; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] FOLFOX = oxaliplatin, leucovorin, and fluorouracil; FU = Follow-up; HCG = human chorionic gonadotropin; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MRI = magnetic resonance imaging; [redacted] SAE = serious adverse event; concentration; [redacted] WOCBP = women of childbearing potential

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs, except for body imaging, [redacted] and pregnancy testing.

Table 2-4: Follow-up Assessments - All Participants (CA224060)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		Weight, BP, HR, and temperature. Targeted physical examination to be performed only as clinically indicated.
Serious Adverse Events Assessments	X		Assessed using NCI CTCAE v5
Adverse Events Assessment	X		Assessed using NCI CTCAE v5
Review of Subsequent Cancer Therapy	X	X	
Laboratory Tests	See Note		For Follow-up Visit 1, including Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1. Repeat at Follow-up Visit 2 if study treatment related toxicity persists.
Pregnancy Test (WOCBP only)	See Note		Serum or urine pregnancy testing is only required at FU1 and FU2 visits, unless increased frequency and duration is required per local regulations.
[redacted]			

Table 2-4: Follow-up Assessments - All Participants (CA224060)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits[b]	Notes
[redacted]			
Efficacy Assessments			
Body imaging	See Note	See Note	See Section 9.1.1. For participants who discontinue study drug for reasons other than PD, follow-up scans should be performed every 6 weeks (± 7 days) up to and including Week 48, then every 12 weeks (± 7 days) until BICR confirmed PD, lost to follow-up, or withdrawal of consent. Radiographic assessments should be Q12W in Follow-Up and not be delayed until follow-up visits 1 & 2.
Brain Imaging	See Note	See Note	See Section 9.1.1. Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks), or sooner if clinically indicated

Abbreviations: [redacted] FU = Follow-up; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; [redacted] WOCBP = women of childbearing potential

[a] Follow-up visits occur as follows: Follow-up Visit 1 = 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose. Follow-up Visit 2 = 100 days (± 7 days) from last dose of study treatment. Participants must be followed for at least 100 days after last dose of study treatment. Both Follow-up visits should be conducted in person.

[b] Survival follow-up visits may be conducted in clinic or by phone. The first survival follow-up visit will occur 3 months (± 14 Days) after Follow-up Visit 2, subsequent survival follow-up visits will occur every 3 months (± 14 days) thereafter. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts.

3 INTRODUCTION

CA224060 is a Phase 2, randomized, open-label study of BMS-986213 (fixed-dose combination [FDC] relatlimab/nivolumab at a 1:3 ratio) in combination with investigator's choice chemotherapy, versus nivolumab in combination with investigator's choice chemotherapy, as first-line (1L) treatment in participants with untreated, unresectable, and either locally advanced or metastatic gastric cancer (GC) or gastroesophageal junction (GEJ) adenocarcinoma. Relatlimab is a fully human lymphocyte activation gene 3 (LAG-3) specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. Relatlimab binds to LAG-3 with high affinity and inhibits binding of this receptor to cells bearing its ligand, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. Relatlimab binding inhibits the negative regulatory function of LAG-3 in vitro. By blocking the normal downregulatory pathway, relatlimab enhances the antitumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered in combination with other therapeutic immuno-oncology (IO) monoclonal antibodies (mAbs).

Nivolumab is a human mAb (IgG4-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[1] Binding of PD-1 to its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

This Phase 2 study for BMS-986213 in GC and GEJ cancer will allow for direct comparison of the treatment effect of BMS-986213 in combination with investigator's choice chemotherapy, versus nivolumab in combination with investigator's choice chemotherapy, as measured by objective response rate (ORR) and duration of response (DOR) in participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma. The study will enroll patients with LAG-3 (+) and LAG-3 (-) expression status (≥ 1% or < 1%; no indeterminate allowed). [redacted] This clinical equipoise is further supported by the fact that the relationship between the immunogenic effects of chemotherapy and the clinical efficacy of immunotherapy has not been well characterized. Accordingly, participants will have their LAG-3 status (≥ 1% or < 1%; no indeterminate allowed) determined prior to randomization, and enrollment into the 2 treatment arms for this study will be stratified based on LAG-3 expression status.

[redacted]

[redacted]

[redacted]

3.2.1 Research Hypothesis

In participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma, the administration of relatlimab plus nivolumab, in combination with chemotherapy, will improve ORR compared to nivolumab in combination with chemotherapy in the LAG-3 positive population.

[redacted]

[redacted]

3.3 Benefit-risk Assessment

Patients with advanced or metastatic GC and GEJ cancer present a significant unmet medical need.

[redacted]

[redacted]

The combination of relatlimab and nivolumab has been evaluated and appears to have a safety profile similar to nivolumab monotherapy. [redacted]

A pattern of immune-mediated adverse events (IMAEs) has been defined for treatment with nivolumab monotherapy and nivolumab in combination with other immune-targeting agents such as relatlimab. Management algorithms have been developed for these events and are provided in Appendix 8. Most high-grade immune-related adverse events are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as detailed in these algorithms.

Additional details on the safety profiles of relatlimab and nivolumab, including results from other clinical studies, are also available in the relatlimab, nivolumab, and BMS-986213 (relatlimab/nivolumab FDC) IBs.

The safety profile of nivolumab combined with oxaliplatin and fluoropyrimidine reflects the additive toxicity of nivolumab monotherapy and chemotherapy, and no new safety signal was identified. The ongoing internal and external studies of PD-L1 inhibitors in combination with chemotherapy in treatment-naïve advanced GC/GEJ participants suggest that this combination is tolerable and manageable, as no new safety signals have been detected.

[redacted]

To ensure an ongoing favorable risk/benefit assessment for participants enrolled in CA224060, an independent Data Monitoring Committee (DMC) will be utilized to evaluate the safety and efficacy of the treatments throughout the conduct of the trial.

This study involves investigational (relatlimab) and approved (nivolumab) drugs whose effects on pregnancy are not yet known or fully defined. Contraception is therefore required for participants who are women of childbearing potential (WOCBP), males, and for female partners of male participants who are WOCBP. These contraception guidelines (see Appendix 4) apply to all female participants and partners of male participants who could be exposed to the drug and who could become pregnant both during treatment and during a defined period after study drug treatment.

The combination of relatlimab and nivolumab, or nivolumab in combination with chemotherapy, has been tested in patients with GC, with promising preliminary data. [redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To compare ORR of BMS-986213 in combination with chemotherapy, with ORR of nivolumab in combination with chemotherapy, by BICR, in randomized participants with untreated, unresectable, and either locally advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma.	• ORR in participants who are LAG-3 positive. ORR is defined as the number of participants with a BOR of CR or PR divided by the number of randomized participants in each arm. BOR is defined as the best response designation as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression (per Response Evaluation Criteria in Solid Tumors [RECIST 1.1]), death due to any cause, or the date of subsequent anticancer therapy, whichever occurs first.
Secondary	
• To assess the overall safety and tolerability of BMS-986213 in combination with chemotherapy vs. nivolumab in combination with chemotherapy in treated participants with advanced or metastatic GC or GEJ cancer.	• The incidence of AEs, SAEs, AE leading to discontinuation, deaths, and laboratory abnormalities in each arm.
• To compare ORR of BMS-986213 in combination with chemotherapy, with ORR of nivolumab in combination with chemotherapy, as assessed by investigator, in randomized participants with untreated, unresectable, and either locally advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma.	• ORR is defined as above, as the number of participants with a BOR of CR or PR as assessed by the investigator using RECIST 1.1, divided by the number of randomized participants in each Treatment Arm.
• To compare ORR by BICR and by investigator of BMS-986213 in combination with chemotherapy with ORR of nivolumab in combination with chemotherapy in randomized participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma, and overall (across LAG-3 negative and positive groups).	• ORR in the LAG-3 negative group or overall is defined as above, as the number of participants in each population with a BOR of CR or PR divided by the number of randomized participants in each Treatment Arm, for that population.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
• To estimate DOR of BMS-986213 in combination with chemotherapy and DOR of nivolumab in combination with chemotherapy in randomized participants with advanced or metastatic LAG-3 positive GC or GEJ adenocarcinoma, by BICR and by the investigator.	• DOR (based on BICR and investigator) is defined as the time between the date of first documented response (CR or PR) to the date of the first PD, per RECIST 1.1, death due to any cause, or the date of subsequent anticancer therapy whichever occurs first.
• To estimate DOR of BMS-986213 in combination with chemotherapy and DOR of nivolumab in combination with chemotherapy in randomized participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma, and in the overall population by BICR and by the investigator.	• DOR in participants with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma and for participants in the overall population (across the LAG-3 groups) is defined as above.
• To assess the difference in the overall survival (OS) of BMS-986213 in combination with chemotherapy and OS of nivolumab in combination with chemotherapy in randomized participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma separately in the LAG-3 positive and LAG-3 negative groups and overall.	• OS is defined as the time between the date of randomization and the date of death. For those without documentation of death, OS will be censored on the last date the participant was known to be alive.
• To assess the difference in the PFS of BMS-986213 in combination with chemotherapy and PFS of nivolumab in combination with chemotherapy as assessed by BICR and investigator in randomized participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma separately in the LAG-3 positive and LAG-3 negative groups and overall.	• PFS is defined as the time between the date of randomization and the date of the first documented PD per BICR or investigator or death due to any cause. Participants who die without a reported prior PD per BICR or investigator (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Those who did not have documented PD per RECIST 1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of subsequent anticancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of subsequent anticancer therapy) will be censored at the randomization date. Those who started any subsequent anticancer therapy without a prior reported PD will be censored at the last tumor assessment prior to or on the initiation of the subsequent anticancer therapy. Participants receiving treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

Table 4-1: Objectives and Endpoints

[redacted]

Abbreviations: [redacted] AE = adverse event; BICR = blinded independent central review; BOR = best overall response; CR = complete response; [redacted]

[redacted] DOR = duration of response; [redacted] GC = gastric cancer; GEJ = gastroesophageal junction; LAG-3 = lymphocyte activation gene 3; [redacted] ORR = objective response rate; OS = overall survival; [redacted] PD = disease progression; PFS = progression-free survival; [redacted] PR = partial response; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event [redacted].

5 STUDY DESIGN

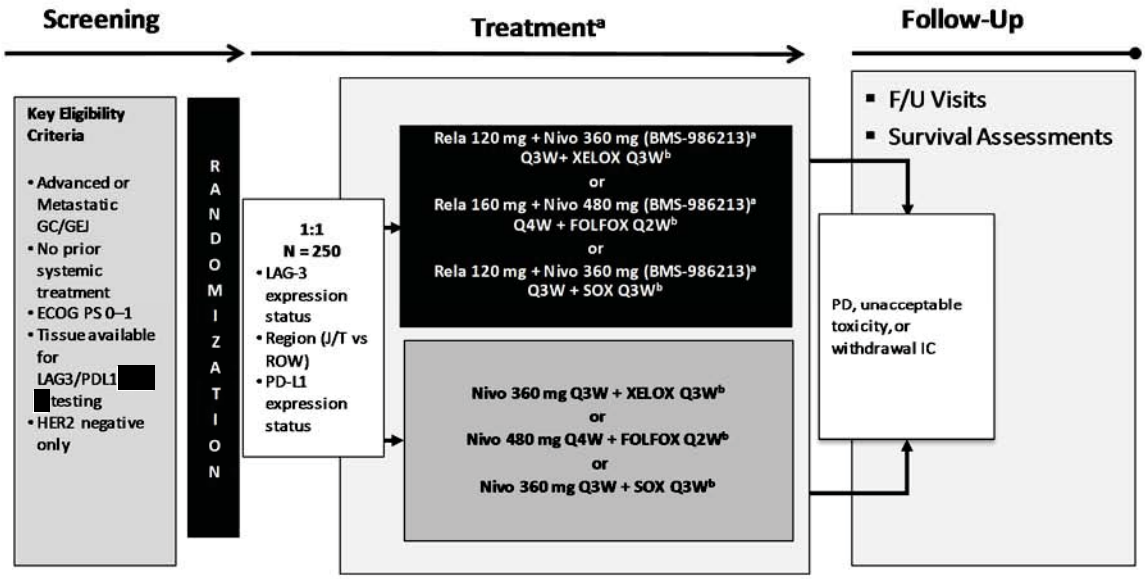
5.1 Overall Design

This is a Phase 2, randomized, open-label, 2-arm study of BMS-986213 or nivolumab in combination with investigator's choice chemotherapy as L1 treatment in participants with untreated, unresectable, and either locally advanced or metastatic GC or GEJ adenocarcinoma. Approximately 250 participants will be randomized in 2 treatment arms in this global clinical study. Nivolumab monotherapy will be administered IV as either 360 mg every 3 weeks (Q3W) or 480 mg every 4 weeks (Q4W), depending on the assigned chemotherapy regimen. Relatlimab and nivolumab combination, as an FDC, will be administered as 120-mg relatlimab/360-mg nivolumab Q3W or 160-mg relatlimab/480-mg nivolumab Q4W, depending on the assigned chemotherapy regimen.

After signing the informed consent form, participants will enter the Screening Phase. A pre-treatment tumor sample is required to be submitted from all participants. Although this study will enroll participants regardless of their LAG-3 expression status (≥ 1% or < 1%; no indeterminate allowed), participants must have their LAG-3 status determined prior to completion of the remaining Screening procedures. **Patients with an indeterminate LAG-3 expression status cannot be enrolled in the study.** As deemed appropriate by the Investigator, participants may complete the remaining Screening procedures in parallel to the determination of the LAG-3 status in order to minimize the duration of the Screening Phase.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



[a] Fixed dose combination of relatlimab [anti-LAG-3] plus nivolumab
[b] Investigator Choice Chemo:

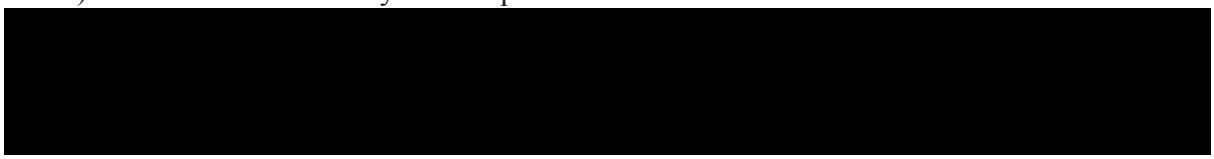
1. **XELOX:** oxaliplatin 130 mg/m² administered IV on Day 1 of each treatment cycle and capecitabine 1000 mg/m² administered orally twice daily on Days 1 to 14 of each treatment cycle, every 3 weeks
2. **FOLFOX:** oxaliplatin 85 mg/m², leucovorin 400 mg/m² and fluorouracil 400 mg/m² administered IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily or per local standard on Days 1 and 2 of each treatment cycle, every 2 weeks.
3. **SOX:** oxaliplatin 130 mg/m² administered IV on Day 1 of each treatment cycle and oral S-1 twice daily on Day 1 to 14 of each treatment cycle, every 3 weeks. S-1 dose was calculated according to body surface area (BSA, mg/m²/dose): BSA <1.25 m², 40 mg/dose; ≥1.25 and <1.5 m², 50 mg/dose; ≥1.5 m², 60mg/dose.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; F/U = follow-ip; GC = gastric cancer; GEJ = gastroesophageal junction; IC = informed consent; J = Japan; LAG-3 = lymphocyte activation gene 3; PD-L1 = programmed death-ligand 1; PS = performance status; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; T = Taiwan; ROW = Rest of World

5.1.1 Screening Phase

- The Screening Phase begins by establishing the participant's initial eligibility and signing of the informed consent form within 28 days of randomization.
- Participants are enrolled using the Interactive Response Technology (IRT) system.
- A pre-treatment tumor sample is required to be submitted from all participants. The participant's tumor-associated immune cells must have an evaluable LAG-3 status (≥ 1% or < 1%; no indeterminate allowed) and must have a PD-L1 status (combined positive score [CPS] < 1 or indeterminate, CPS ≥ 1 to < 5, CPS ≥ 5). LAG-3 expression status (LAG-3 [+] or LAG-3 [-]) and PD-L1 expression status must be determined by the central lab **prior to completion of the remaining screening procedures**. As deemed appropriate by the investigator, participants may complete the remaining screening procedures in parallel to the determination of the LAG-3 and PD-L1 expression in order to minimize the duration of the Screening Phase.
- Sufficient tumor tissue (either a formalin-fixed, paraffin-embedded [FFPE] tissue block or minimum 20 positively charged slides [if 20 are not obtainable, discuss with Sponsor]) must be submitted for biomarker evaluation prior to randomization. If available, the pathology report should be submitted with the FFPE tissue block or unstained tumor tissue slides. The tumor tissue sample may be fresh or archival if obtained within 3 months prior to randomization, and

there cannot have been any systemic therapy given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. If insufficient tumor tissue is provided for analysis, acquisition of additional tumor tissue (block and/or slides) for the biomarker analysis is required.



- Participant is assessed for study eligibility according to the inclusion (Section 6.1) and exclusion (Section 6.2) criteria. The detailed procedures are described in Table 2-1.

5.1.2 Treatment Phase

- The Treatment Phase begins after contacting the IRT system for randomization. The choice of chemotherapy regimen (XELOX, SOX, or FOLFOX) must be decided before contacting the IRT system for randomization.
- Participants will be randomized to either the BMS-986213 or nivolumab arm. Each arm will be given in combination with investigator's choice chemotherapy (XELOX, FOLFOX, or SOX).
- The treatment will be given until disease progression (PD) (see Section 7.3.8), unacceptable toxicity, or participant withdrawal of consent, whichever comes first.
- Stratification factors for this study are as follows:
  - LAG-3 expression (≥ 1% or < 1%; no indeterminate allowed)
  - Region (Japan/Taiwan [J/T] vs rest of world [ROW])
  - PD-L1 expression status (CPS < 1 or indeterminate, CPS ≥ 1 to < 5, CPS ≥ 5).
- Administration of study treatment is to begin within 3 calendar days of randomization.
- Each cycle will be 6 weeks in duration.
- On the day of infusion, BMS-986213 or nivolumab is to be administered first, followed by chemotherapy. The administration procedures of chemotherapy will follow local standards. **BMS-986213 or nivolumab and chemotherapy should be administered on the same day, with the following exceptions:**
  - BMS-986213 or nivolumab is allowed to be administered alone in cases where the chemotherapy has been delayed or discontinued due to toxicity.
  - Chemotherapy alone is allowed to be administered in cases where BMS-986213 or nivolumab has been delayed or discontinued due to toxicity.
  - Participants assigned to FOLFOX will have only FOLFOX administered on Day 15 of the odd-numbered cycles (ie, Cycles 1, 3, 5, etc) and Day 1 and 29 of the even-numbered cycles (ie, Cycles 2, 4, 6, etc).
- No cross-over is allowed between XELOX, SOX, and FOLFOX regimens.
- The Treatment Phase ends when the participant is discontinued from study therapy (ie, PD, unacceptable toxicity, or participant withdrawal of consent).

Study assessment data are to be collected as outlined in Table 2-2 and Table 2-3.

5.1.3 Follow-up Phase

- The Follow-up Phase begins when the decision is made to discontinue a participant from study therapy.
- Follow-up Visit 1 will be performed 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose. Follow-up Visit 2 will be performed 100 days (± 7 days) from last dose of study treatment. Participants must be followed for at least 100 days after last dose of study treatment. Both follow-up visits should be conducted in person.
- Survival visits - The first survival follow-up visit will be performed 3 months (± 14 days) after follow-up Visit 2. Subsequent survival follow-up visits will occur every 3 months (± 14 days) thereafter. Survival follow-up visits may be conducted in clinic or by phone.

Study follow-up assessment data are to be collected as outlined in Table 2-4.

5.1.4 Blinded Independent Central Review

A Blinded Independent Central Review (BICR) will be utilized in this study for determination of BICR-assessed endpoints. The BICR will review all available tumor assessment scans for all treated participants. All investigator determinations of PD will be reviewed by the BICR (see Section 9.1.4). Details of BICR responsibilities and procedures will be specified in the BICR charter.

5.1.5 Data Monitoring Committee

A DMC will be established to provide oversight of safety and efficacy considerations in protocol CA224060 and to provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available safety and efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Additional details concerning DMC oversight are provided in the DMC charter.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

5.2 Number of Participants

It is expected that approximately 420 participants will need to be enrolled in order to randomize 250 participants.

Approximately 250 participants are planned to be randomized 1:1 to 1 of 2 treatment arms:

1) BMS-986213 in combination with investigator's choice chemotherapy
2) Nivolumab in combination with investigator's choice chemotherapy

See Section 10.1 for sample size determination and associated assumptions.

5.3 Study Definitions

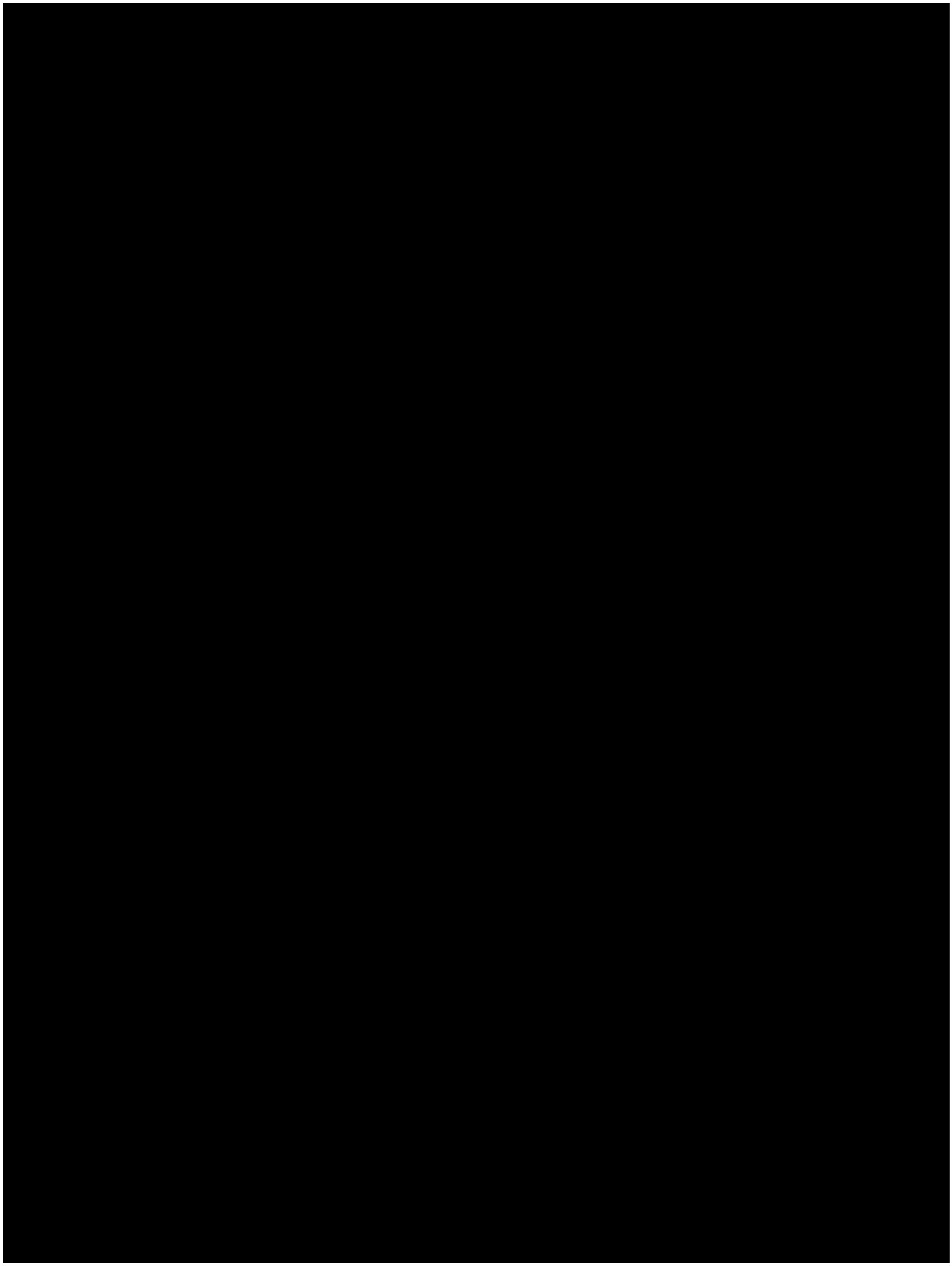
The start of the trial is defined as the first visit for the first participant screened. The End of Trial for the primary endpoint of ORR is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant for the corresponding endpoint.

Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The duration of the study, from start of randomization to primary endpoint ORR analysis, is expected to be approximately 22 months, assuming 16 months accrual duration. Additional follow-up for progression-free survival (PFS) and overall survival (OS) may be conducted up to approximately 5 years for OS after the randomization of the last participant. The study will end once survival follow-up has concluded. Under some circumstances, participants may not be followed for 5 years for survival in this study (eg, the participants may be offered to enroll into a roll-over study, or the sponsor may terminate the study early).

[redacted]

[redacted]



[redacted]

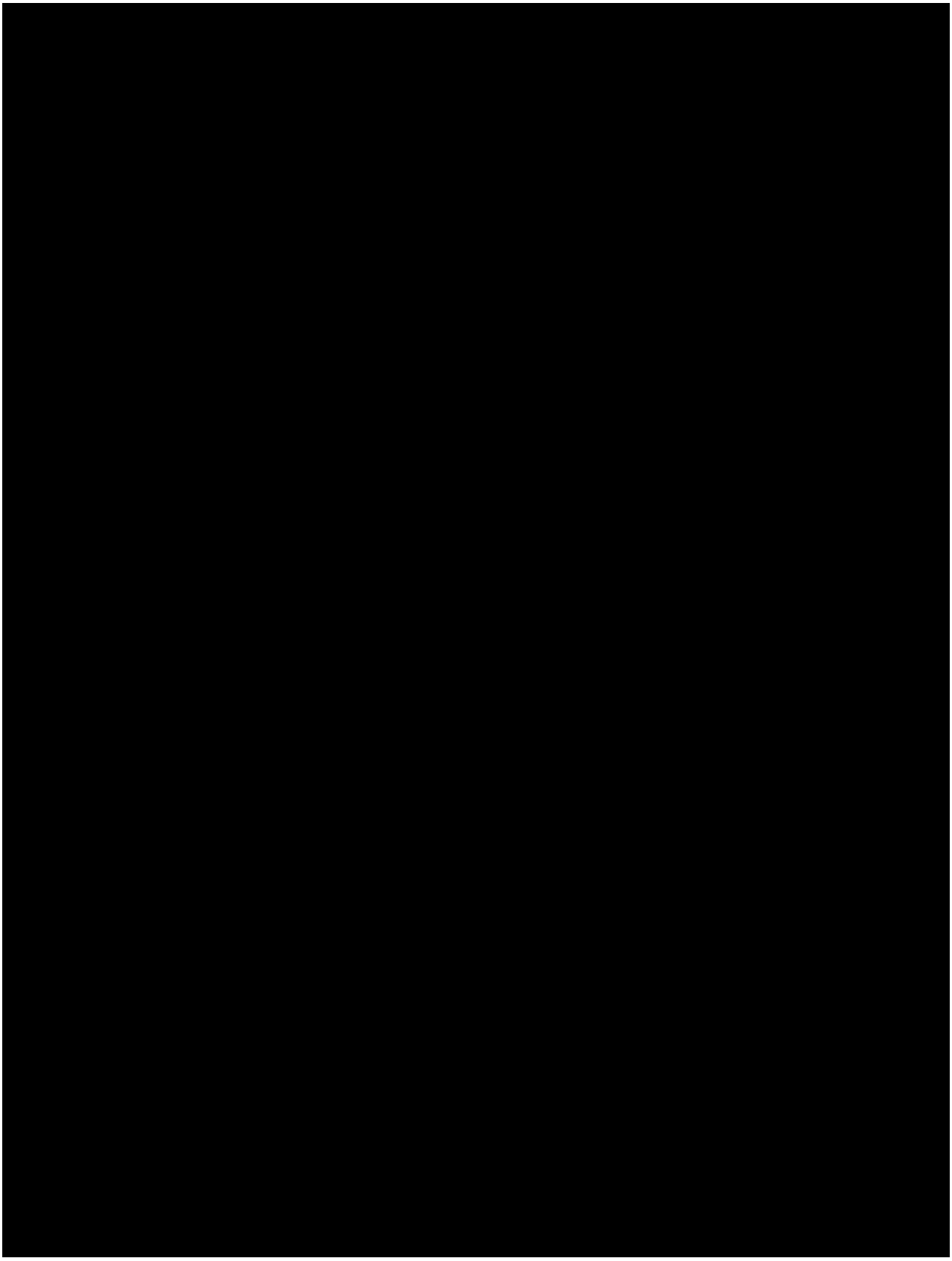
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an institutional review board/independent ethics committee (IRB/IEC)-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) All participants must have histologically or cytologically confirmed diagnosis of unresectable and either locally advanced or metastatic GC or GEJ adenocarcinoma. The documentation of GC or GEJ involvement can include biopsy, endoscopy, or imaging.

b) Participant must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for unresectable and either locally advanced or metastatic gastric or GEJ adenocarcinoma

c) Allowed Prior Therapies: Prior adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy for GC or GEJ cancer are permitted, as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization. Chinese traditional medicines with an approved indication of cancer treatment are permitted as long as the last administration occurred at least 2 weeks prior to randomization.

d) Participant must have at least 1 measurable lesion by CT or MRI per RECIST 1.1 criteria; radiographic tumor assessment should be performed within 28 days prior to randomization.

e) ECOG performance status score of 0 or 1 (Appendix 6).

f) Tumor tissue must be provided for biomarker analyses. In order to be randomized, the participant's tumor-associated immune cells must have an evaluable LAG-3 status (≥ 1% or < 1%; no indeterminate allowed) and must have a PD-L1 status (CPS < 1 or indeterminate, CPS ≥ 1 to < 5, CPS ≥ 5). Participants whose tumor-associated immune cells are LAG-3 indeterminate will not be randomized to a treatment arm. Either a FFPE tissue block or minimum 20 positively charged slides (if a minimum of 20 slides is not obtainable, discuss with Sponsor) must be submitted for biomarker evaluation prior to randomization. If available, the pathology report should be submitted with the FFPE tissue block or unstained tumor tissue slides. The tumor tissue sample may be fresh or archival if

obtained within 3 months prior to randomization, and there can have been no systemic therapy given after the sample was obtained. Tissue must be a core needle, excisional, or incisional biopsy.

g) Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

3) Age and Reproductive Status

a) Males and females, ≥ 18 years of age or age of majority.

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment(s) plus 24 weeks after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment(s) plus 33 weeks after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4) that have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) HER2 positive status (IHC3+ or FISH positive [HER2:CEP17 ratio > 2] or IHC2+/FISH+).

b) Participants with untreated known central nervous system (CNS) metastases. Participants are eligible if CNS metastases have been adequately treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, participants must be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

c) Prior malignancy active within the previous 3 years, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

d) Participants with an active, known, or suspected autoimmune disease. Participants with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

f) All toxicities attributed to prior anticancer therapy other than hearing loss, alopecia, and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5) or baseline before administration of study drug.

g) Participants with > Grade 1 peripheral neuropathy.

h) Participants with ascites that cannot be controlled with appropriate interventions.

i) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

   i) Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent

   ii) Uncontrolled angina within the 3 months prior to consent

   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes or poorly controlled atrial fibrillation)

   iv) QTc prolongation > 480 msec

   v) History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled venous thrombosis, etc)

   vi) Cardiovascular disease-related requirement for daily supplemental oxygen

   vii) History of 2 or more MIs OR 2 or more coronary revascularization procedures

   viii) Participants with history of myocarditis, regardless of etiology

   ix) Left ventricular ejection fraction (LVEF) <50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition (MUGA) scan (TTE is preferred test) within 6 months prior to date of first study drug administration.

j) Participants with serious or uncontrolled medical disorders.

k) Participants must have recovered from the effects of major surgery requiring general anesthetic or significant traumatic injury at least 14 days prior to randomization.

2) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.

b) Prior treatment with relatlimab or any other LAG-3-targeted agents.

c) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.6.1 for prohibited therapies.

d) Participants who have received a live/attenuated vaccine within 30 days of first treatment.

3) Physical and Laboratory Test Findings

a) White blood cells < 2000/μL (SI: < 2.00 × 109/L)

b) Neutrophils < 1500/μL (SI: < 1.50 × 109/L)

c) Platelets < $100*10^3$/μL (SI: < 100 × 109/L) (transfusions not permitted within 72 hours prior to qualifying laboratory value)

d) Hemoglobin < 9.0 g/dL (SI:< 90 g/L) (transfusions not permitted within 72 hours prior to qualifying laboratory value)

e) Serum creatinine > 1.5 × upper limit of normal (ULN) or calculated creatinine clearance < 50 mL/min (using the Cockcroft-Gault formula):

$$\text{Female creatinine clearance (CrCl)} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

f) AST or ALT: > 3.0 × ULN (or > 5.0 x ULN if liver metastases are present)

g) Total bilirubin > 1.5 × ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 × ULN)

h) Troponin T (TnT) or I (TnI) > 2 × institutional ULN. TnT or TnI levels between > 1 to 2 × ULN will be permitted to participate in the study if a repeat assessment remains within ULN or patient has no cardiac symptoms and participant undergoes a cardiac imaging evaluation found to have no significant myocardial disease or dysfunction. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible.

i) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus (eg, Hepatitis B surface antigen [Australia antigen] positive, or Hepatitis C virus antibody [anti-HCV] positive [except if HCV-ribonucleic acid (RNA) negative]).

j) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. NOTE: Testing for HIV must be performed at sites where mandated locally.

k) Positive pregnancy test at enrollment or prior to administration of study medication.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

b) Any contraindications to any of the study drugs of the chemotherapy regimen (XELOX, SOX, or FOLFOX) selected by the investigator. Investigators should refer to local package insert of the chemotherapy drugs.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.)

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

No restrictions are required for BMS-986213 or nivolumab.

Please also refer to the XELOX, SOX, and FOLFOX package inserts for possible restrictions.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-in Period

This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Screening Assessments - All screening tests for participants may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant (see Table 2-1).

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- relatlimab/nivolumab FDC solution for injection
- nivolumab solution for injection
- oxaliplatin concentrate for solution for infusion
- capecitabine tablets
- fluorouracil solution for injection
- leucovorin (folinic acid) solution for injection
- tegafur/gimeracil/oteracil capsule

An investigational product (IP; also known as investigational medicinal product in some regions) is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Investigational products used in this trial are provided in Table 7-1. There are no non-investigational products in this study.

Table 7-1: Study Treatments for CA224060

Product Description/Class and Dosage Form	Potency	IP/ Non-IMP	Packaging/Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection[a]	10 mg/mL	IP	10-mL vial. Clear to opalescent, colorless to pale yellow liquid. May contain particles.	Refer to the label on container and/or pharmacy manual
BMS-986213 (Relatlimab 80 mg/ Nivolumab 240 mg) Solution for Injection[b]	16 mg/mL	IP	20-mL vial. Colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present.	Refer to the label on container and/or pharmacy manual
Oxaliplatin Concentrate for Solution for Infusion[c]	5 mg/mL	IP	Clear, colorless solution (20 mL/ vial), 1 vial/carton	Refer to the label on container and/or pharmacy manual
Capecitabine[c] Tablet	150 mg and 500 mg	IP	Wallet/blister card containing 10, 20, or 30 tablets	Refer to the label on container and/or pharmacy manual
Fluorouracil Solution for Injection[c]	50 mg/mL	IP	Clear, colorless, or almost colorless solution. 50 mL/vial (1 vial/carton)	Refer to the label on container and/or pharmacy manual
Leucovorin (folinic acid) Solution for Injection[c]	50 mg/mL	IP	8 mL/vial (1 or 4 vials/carton)	Refer to the label on container and/or pharmacy manual
S-1 tegafur/gimeracil/oteracil[c] Capsule	20 mg/5.8 mg/15.8 mg	IP	PCTFE/PVC/Alopaque blisters containing 14 capsules each. Each pack contains 84 capsules.	Refer to the label on container and/or pharmacy manual
S-1 tegafur/gimeracil/oteracil[c] Capsule	15 mg/4.35 mg/11.8 mg	IP	PCTFE/PVC/Alopaque blisters containing 14 capsules each. Each pack contains 84 capsules.	Refer to the label on container and/or pharmacy manual

Abbreviations: IP = investigational product; N/A = not applicable; PCTFE = polychlorotrifluoroethylene; PVC = polyvinyl chloride.

[a] May be labeled as either "BMS-936558-01" or "Nivolumab."

[b] Relatlimab/nivolumab combination is also referred to BMS-986213.

[c] These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. In these cases, products may be in a different pack size/potency/pharmaceutical form than listed in the table. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics.

7.1 Treatments Administered

7.1.1 BMS-986213 or Nivolumab Dosing

BMS-986213 (prepared in normal saline for relatlimab 120 mg/nivolumab 360 mg or relatlimab 160 mg/nivolumab 480 mg), nivolumab (360 or 480 mg) dosing is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore-size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Instructions for dilution and infusion of BMS-986213 and nivolumab injection will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Participants should receive BMS-986213 or nivolumab as a 1-hour infusion or 30-minute infusion, respectively, on the days outlined in Table 7.1.2-1, Table 7.1.3-1, and Table 7.1.4-1 based on the specific chemotherapy regimen. Treatment will be given until PD, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

There will be no dose escalations or reductions of BMS-986213 or nivolumab. Participants may be dosed within a ± 3 day window. Premedication for potential infusion reaction is not recommended for the first dose of either treatment.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.3.10.

Doses of BMS-986213 or nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Resumption of treatment should be at the next scheduled time point. Dosing visits are not skipped, only delayed.

Infusions are compatible with PVC or polyolefin containers and infusion sets and glass bottles.

For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual.

When BMS-986213 or nivolumab are to be administered on the same day as the chemotherapy, BMS-986213 or nivolumab are to be administered first. BMS-986213 or nivolumab infusion must be promptly followed by a diluent flush to clear the line of IP before starting the chemotherapy infusion(s). The second infusion will always be the chemotherapy study drug(s) and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred. The time between immunotherapy and chemotherapy infusions is expected to be approximately 30 minutes, but may be more or less depending on the situation.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.1.2 Dose Schedule for BMS-986213 or Nivolumab Plus XELOX

Participants assigned to XELOX will receive BMS-986213 (relatlimab 120 mg/nivolumab 360 mg) or nivolumab 360 mg, administered IV over 60 minutes or 30 minutes, respectively, oxaliplatin 130 mg/m^2 administered IV on Days 1 and 22 of each 6-week treatment cycle, and

capecitabine 1000 mg/m^2 administered orally twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening) on Days 1 to 14 and Days 22 to 35 of each 6-week treatment cycle (see Table 7.1.2-1). Immunotherapy treatment should be administered first, prior to chemotherapy treatment. Dosing windows for subsequent XELOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

Premedication for potential infusion reaction is not recommended for the first dose of either treatment. Premedication maybe administered for nausea and vomiting prophylaxis, after the completion of the immunotherapy treatment or, in the absence of preceding immunotherapy, before chemotherapy administration, as clinical presentation warrants and per local standard.

Capecitabine should be taken with food.

Participants should be provided with drug diaries at each visit and instructed to record intake of capecitabine in the diary after each twice daily administration.

Table 7.1.2-1: Dose Schedule for BMS-986213 or Nivolumab Plus XELOX

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 7)	Cycle 3 (Week 13)	Cycle 4 (Week 19)	Cycle 5 (Week 25) until EOT (Every 6 weeks)
BMS-986213 or nivolumab in combination with XELOX	BMS-986213 (relatlimab 120 mg/nivolumab 360 mg), nivolumab 360 mg	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22
	Oxaliplatin 130 mg/m^2	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22
	Capecitabine 1000 mg/m^2 twice daily (ie, 1000 mg/m^2 in the morning and 1000 mg/m^2 in the evening)	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35

7.1.3 Dose Schedule for BMS-986213 or Nivolumab Plus FOLFOX

- Participants assigned to FOLFOX will receive BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) or nivolumab 480 mg, administered IV over 60 minutes or 30 minutes, respectively, on Days 1 and 29 of every odd-numbered 6-week treatment cycle (Cycle 1, 3, 5, etc) and Day 15 of every even numbered 6-week treatment cycle (Cycle 2, 4, 6, etc). Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 will be administered IV on Days 1, 15, and 29 of each 6-week treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily (or per local standard) on Days 1 and 2, 15 and 16, and 29 and 30 of each 6-week treatment cycle (see Table 7.1.3-1). As a consequence of this dosing regimen, FOLFOX will be administered alone, without immunotherapy, on Day 15 of each odd numbered 6-week

treatment cycle and Days 1 and 29 of each even numbered 6-week treatment cycle. Immunotherapy treatment should be administered first, prior to chemotherapy treatment. Dosing windows for subsequent FOLFOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

Premedication for potential infusion reaction is not recommended for the first dose of either treatment. Premedication maybe administered for nausea and vomiting prophylaxis, after the completion of the immunotherapy treatment or, in the absence of preceding immunotherapy, before chemotherapy administration, as clinical presentation warrants and per local standard.

Table 7.1.3-1: Dose Schedule for BMS-986213 or Nivolumab Plus FOLFOX

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 7)	Cycle 3 (Week `13)	Cycle 4 (Week 19)	Odd Cycles Starting at Cycle 5 (Week 25) until EOT	Even Cycles Starting at Cycle 6 (Week 31) until EOT
BMS-986213 or nivolumab in combination with FOLFOX	BMS-986213 (relatlimab 160 mg/nivolumab 480 mg), or nivolumab 480 mg,	Days 1 and 29	Day 15	Days 1 and 29	Day 15	Days 1 and 29	Day 15
	Oxaliplatin 85 mg/m^2	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29
	Leucovorin 400 mg/m^2	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29
	Fluorouracil 400 mg/m^2	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29	Days 1, 15, 29
	Fluorouracil 1200 mg/m^2	Days 1 & 2, 15 & 16, 29 & 30	Days 1 & 2, 15 & 16, 29 & 30	Days 1 & 2, 15 & 16, 29 & 30	Days 1 & 2, 15 & 16, 29 & 30	Days 1 & 2, 15 & 16, 29 & 30	Days 1 & 2, 15 & 16, 29 & 30

7.1.4 Dose Schedule for BMS-986213 or Nivolumab Plus SOX

Participants assigned to SOX will receive BMS-986213 (relatlimab 120 mg/nivolumab 360 mg) or nivolumab 360 mg, administered IV over 60 or 30 minutes, respectively, and oxaliplatin 130 mg/m^2 administered IV on Days 1 and 22 of each 6-week treatment cycle, and oral S-1 twice daily (ie, 1 dose in the morning and 1 dose in the evening) on Days 1 to 14 and Days 22 to 35 of each 6-week treatment cycle. S-1 (tegafur/gimeracil/oteracil) dose should be administered as calculated according to body surface area (BSA, mg/m^2/dose): BSA < 1.25 m^2, 40 mg/dose; ≥ 1.25 and < 1.5 m^2, 50 mg/dose; ≥ 1.5 m^2, 60 mg/dose (see Table 7.1.4-1). Immunotherapy treatment should be administered first, prior to chemotherapy treatment. Dosing windows for subsequent SOX doses should adhere to recommendations in the prescribing information or local standards, where indicated.

Premedication for potential infusion reaction is not recommended for the first dose of either treatment. Premedication maybe administered for nausea and vomiting prophylaxis, after the completion of the immunotherapy treatment or, in the absence of preceding immunotherapy, before chemotherapy administration, as clinical presentation warrants and per local standard.

Participants should be provided with drug diaries at each visit and instructed to record intake of S-1 in the diary after each twice daily administration.

Table 7.1.4-1 Dose Schedule for BMS-986213 or Nivolumab Plus SOX

Treatment Group	Drug Name	Cycle 1 (Week 1)	Cycle 2 (Week 7)	Cycle 3 (Week 13)	Cycle 4 (Week 19)	Cycle 5 (Week 25) until EOT (Every 6 weeks)
BMS-986213 or nivolumab in combination with SOX	BMS-986213 (relatlimab 120 mg/nivolumab 360 mg) or nivolumab 360 mg	Day 1 and 22	Day 1 and 22	Day 1 and 22	Day 1 and 22	Day 1 and 22
	Oxaliplatin 130 mg/m^2	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22	Days 1 and 22
	S-1 (tegafur/gimeracil /oteracil) (ie, 1 dose in the morning and 1 dose in the evening)	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35	Days 1 to 14 and Days 22 to 35

7.1.5 Crossover for Investigator's Choice Chemotherapy

No crossover will be allowed among the XELOX, FOLFOX and SOX regimens in this study.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by using IRT to obtain the subject number. Every participant who signs the informed consent form must be assigned a subject number in IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

After enrollment in the IRT, participants who have met all eligibility criteria will be randomized through the IRT. The following information is required for participant randomization:

- Subject number
- Year of birth
- LAG-3 status (≥ 1% or < 1%; no indeterminate allowed) provided by the central lab directly to the IRT system
- PD-L1 status (CPS < 1 or indeterminate, CPS ≥ 1 to < 5, CPS ≥ 5) provided by the central lab directly to the IRT system
- Anatomical location (gastric vs GEJ)
- Region (Japan/Taiwan vs ROW)
- The choice of chemotherapy regimen - XELOX, SOX, or FOLFOX

The randomization procedures will be stratified by the following factors: LAG-3 expression (≥ 1% or < 1%; no indeterminate allowed), Region (Japan/Taiwan vs ROW), and PD-L1 expression status (CPS < 1 and indeterminate, CPS ≥ 1 to < 5, or CPS ≥ 5). The exact procedures for using the IRT will be detailed in the IRT manual.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

All participants will be enrolled using the IRT and will be designated a subject number after signing the Pre-Screen informed consent form (ICF). Per the ICF, information that identifies the participant, such as name, will be replaced with a unique code. The Sponsor refers to this coded information as Study Data. Personal information is coded to protect the participants' privacy. The participant's name and identifying information will remain with the study site and will remain confidential at all times.

7.3 Dosage Modification

7.3.1 Dose Modification Criteria for BMS-986213 or Nivolumab Plus Chemotherapy

If AEs are considered to be related to study treatment (BMS-986213 or nivolumab OR chemotherapy), every attempt must be made to attribute the individual study treatment to the AE, if possible, or to the combination regimen.

- For AEs that are deemed to be related to BMS-986213 or nivolumab ONLY by the treating physician, dose delays are permitted (see Section 7.3.5). Dose reductions are not permitted (see Section 7.3.2). The chemotherapy should continue as scheduled.
- For AEs that are deemed to be related to the chemotherapy ONLY by the treating physician, dose modifications are permitted according to local standard or local package insert (see Sections 7.3.3.2 for XELOX, 7.3.3.3 for FOLFOX, and 7.3.3.4 for SOX). BMS-986213 or nivolumab administration should continue as scheduled.
- For AEs that are possibly related to the combination regimen (BMS-986213 or nivolumab PLUS chemotherapy), the most conservative toxicity management guidelines must be followed.
- If there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. Resumption of treatment should be at the next scheduled time point if criteria to resume treatment are met.

7.3.2 Dose Modification Criteria for BMS-986213 or Nivolumab

No dose reduction for BMS-986213 or nivolumab is permitted.

7.3.3 Dose Modification Criteria for Oxaliplatin-Plus-Fluoropyrimidine Treatment

Dose modifications of oxaliplatin, capecitabine, leucovorin, fluorouracil, and tegafur-gimeracil-oteracil are permitted according to local standards or local package inserts.

7.3.3.1 General Guidance for Dose Modification of Chemotherapy

- Treatment for the first cycle should only commence if all the inclusion criteria are met and the participant has been randomized. For subsequent cycles, dose delay/modification is permitted per local standard or as described in Sections 7.3.3.2, 7.3.3.3, and 7.3.3.4.
- Doses of any study drug omitted for toxicity are not replaced or restored. Instead, the patient should resume the planned treatment cycles. Supportive care (for example, colony-stimulating factors [CSFs], blood and blood products, etc) can be administered in accordance with the latest American Society of Clinical Oncology or other equivalent guidelines.
- Dose modification, for nonserious and nonlife-threatening toxicities like alopecia, altered taste, or nail changes, may not be required and the final decision is left to the discretion of the treating investigator.
- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest CTCAE v5 grading.
- If there is a delay or modification in administration of one of the drugs in the chemotherapy regimen due to toxicity, treatment with the other drug(s) in the regimen should continue as

scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

If toxicity related to any component of chemotherapy does not resolve in the same treatment cycle, the administration of that component can be delayed up to 6 weeks. If the toxicity does not resolve within 6 weeks, that component will be discontinued, unless it is determined by the treating investigator that the patient might benefit from continuation of the component.

7.3.3.2 Dose Modification Criteria for XELOX

Capecitabine

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or treatment interruption or dose reduction. Dose modifications of capecitabine are presented in Table 7.3.3.2-1. Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life threatening (eg, alopecia, altered taste, or nail changes), treatment can be continued at the same dose without reduction or interruption. Participants taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced.

Table 7.3.3.2-1: Recommended Dose Modifications of Capecitabine

Toxicity[a]	During a Course of Therapy	Dose Adjustment for Next Treatments (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0 to 1	100% (1000 mg/m^2)
2nd appearance		75% (750 mg/m^2)
3rd appearance		50% (500 mg/m^2)
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0 to 1	75% (750 mg/m^2)
2nd appearance		50% (500 mg/m^2)
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue treatment permanently or, if physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0 to 1	50% (500 mg/m^2)

[a] According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 4.0.

Oxaliplatin

Dose Modifications for Neurotoxicity

- For Grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia), or limiting instrumental activities of daily living, skip oxaliplatin. When toxicity resolves to ≤ Grade 1, resume oxaliplatin at 75% of initial dose. If oxaliplatin is skipped for 4 weeks (2 consecutive doses) for neurologic toxicity, discontinue oxaliplatin.
- For Grade 3 or greater peripheral sensory neuropathy (severe paresthesia or dysesthesia), or limiting self-care activities of daily living, discontinue oxaliplatin.

Dose Modifications for Participants with Renal Impairment

- For normal renal function or mild to moderate renal impairment (CrCl > 50 mL/min), the full dose of oxaliplatin can be administered.
- For severe renal impairment, the oxaliplatin dose should be reduced to 75% of the initial dose.

Dose Modifications for Participants with Hematological Toxicity

- For Grade 2 or Grade 3 thrombocytopenia, oxaliplatin should be reduced to 75% of the initial dose. For Grade 4 thrombocytopenia, the dose should be reduced to 50% of the initial dose.
- For Grade 3 or Grade 4 neutropenia or febrile neutropenia, the oxaliplatin dose should be reduced to 75% of the initial dose.

7.3.3.3 Dose Modification Criteria for FOLFOX

Recommended dose modifications of FOLFOX are provided in Table 7.3.3.3-1 and criteria for dose modification of FOLFOX are provided in Table 7.3.3.3-2.

Table 7.3.3.3-1: Recommended Dose Modifications of FOLFOX

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/48 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/48 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/48 hours

Abbreviation: 5-FU: 5-fluorouracil.

Table 7.3.3.3-2: Criteria for Dose Modifications of FOLFOX

Toxicity	Definition	During a course of therapy	Dose adjustments for next treatments
Neutropenia	Grade 3 or greater	Interrupt until resolved to Grade 2	Dose level -1 *If treatment delayed for 4 consecutive weeks, discontinue all treatment
Thrombocytopenia	Grade 2	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 2 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 3	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 3 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 4	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 4 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
Neurologic toxicity	Grade 2 peripheral sensory neuropathy	Interrupt until resolved to Grade 1	Oxaliplatin dose -1 Continue 5-FU and leucovorin *If oxaliplatin delayed for neurologic toxicity for 4 consecutive weeks, discontinue oxaliplatin, continue 5-FU and leucovorin
	Grade 3 or greater peripheral sensory neuropathy	Discontinue oxaliplatin	Continue 5-FU and leucovorin
Gastrointestinal toxicities	Grade 2 or greater diarrhea	Interrupt until resolved to Grade 1	Dose level -1 If dose delayed for diarrhea for 4 consecutive weeks, discontinue all treatment

For toxicities not listed above, dose modifications are permitted per local standards. Participants may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time and become problematic.

7.3.3.4 Dose Modification Criteria for SOX Including Initiation and Continuation

The dosage and the necessity of treatment interruption should be checked for each participant before the start of each administration in accordance with the following criteria for starting treatment. Decisions on dose interruption and dose reduction should be made on the basis of the latest data available at the time.

Criteria for Starting SOX Therapy

Prior to starting SOX therapy, it must be confirmed whether the participant fulfills the criteria in Table 7.3.3.4-1. If the participant does not meet all of the criteria, the study treatment could be postponed until all of the criteria are met. Note that, even if a participant does not meet 1 or more of the following criteria, SOX therapy may be administered if treatment is expected to lead to clinical benefit, SOX therapy is not contraindicated and can be safely administered to the participant. If any of the criteria for starting SOX therapy are not met at subsequent doses, the dose should be reduced by 1 level, and the acceptability of the administration and the need for postponement will be determined according to the criteria for starting treatment at postreduction doses.

Table 7.3.3.4-1: Criteria for Starting SOX Therapy

Parameter	Criteria
White blood cells	≥ 3000/mm^3 (only for dose of 130 mg/m^2 oxaliplatin)
Neutrophils	≥ 1500/mm^3
Platelets	≥ 100000/mm^3 (only for dose of 130 mg/m^2 oxaliplatin) ≥ 75000/mm^3
AST/ALT	≤ ULN × 2.5 (or ≤ ULN × 5.0 in the presence of liver metastasis)
Serum creatinine	≤ ULN × 1.2
Infection	No fever ≥ 38°C suggesting infection
Diarrhea, stomatitis, Hand-Foot syndrome	Grade ≤ 1

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Criteria for Interruption of SOX Therapy

If any of the criteria in Table 7.3.3.4-2 are met after starting tegafur-gimeracil-oteracil, tegafur-gimeracil-oteracil potassium should be interrupted then resumed after the criteria are met. Doses of tegafur-gimeracil-oteracil potassium omitted for toxicity are not replaced.

Table 7.3.3.4-2: Criteria of Interruption of Tegafur-Gimeracil-Oteracil Potassium

Parameter	Criteria of Interruption of Tegafur-Gimeracil-Oteracil Potassium (Within the Same Treatment Period)
Neutrophils	< 1000/mm^3 (Grade ≥ 3)
Platelets	< 50000/mm^3 (Grade ≥ 3)
AST/ALT	> ULN × 2.5 (or > ULN × 5.0 in the presence of liver metastasis)
Serum creatinine	> ULN × 1.2
Infection	Fever ≥ 38°C suggesting infection

Table 7.3.3.4-2: Criteria of Interruption of Tegafur-Gimeracil-Oteracil Potassium

Parameter	Criteria of Interruption of Tegafur-Gimeracil-Oteracil Potassium (Within the Same Treatment Period)
Diarrhea, stomatitis, Hand-Foot syndrome	Grade ≥ 2

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Criteria for Dose Reduction of SOX Therapy

On the planned day of administering SOX therapy, it must be confirmed whether the participant fulfills the criteria in Table 7.3.3.4-3. If the participant meets any of the criteria at any time during the last dose and start of subsequent dose, 1 or both agents must be reduced according to Table 7.3.3.4-4 and be continued. Once the dose has been reduced, it should not be increased at a later time.

Table 7.3.3.4-3: Criteria for Dose Reduction of SOX Therapy

Adverse Events		Next Doses	
Parameter	**Criteria**	**Oxaliplatin**	**Tegafur-Gimeracil-Oteracil Potassium**
Decreased platelet count	(only for dose of 130 mg/m^2 oxaliplatin) Not met ≥ 100000/mm^3 within 7 days of planned date of dosing	1-level reduction	-
	Not met ≥ 75000/mm^3 (Grade ≤ 1) within 7 days of planned date of dosing		
	(only for dose of 50 mg/m^2 oxaliplatin) Not met ≥ 75000/mm^3 (Grade ≤ 1) within 7 days of planned date of dosing	-	1-level reduction
	< 25000/mm^3 (Grade 4)	1-level reduction	1-level reduction
Decreased neutrophil count	< 500/mm^3 (Grade 4)	1-level reduction	1-level reduction
Febrile neutropenia	Neutrophil count < 1000/mm^3 with fever ≥ 38°C (axillary temperature)	1-level reduction	1-level reduction
Diarrhea, stomatitis, Hand-Foot syndrome	Grade ≥ 3	1-level reduction	1-level reduction
Allergic reaction/hypersensitivity suspected to be due to	Grade ≥ 3	Discontinued	-

Table 7.3.3.4-3: Criteria for Dose Reduction of SOX Therapy

Adverse Events		Next Doses	
Parameter	**Criteria**	**Oxaliplatin**	**Tegafur-Gimeracil-Oteracil Potassium**
administration of oxaliplatin			
Peripheral neuropathy	Grade 2	1-level reduction	-
	Grade 3	Skip dosing[a]	-
	Grade 4	Discontinued	-

[a] Resume dosing from 1-level reduction after recovering Grade 2 or less.

Table 7.3.3.4-4: Doses of SOX Therapy for Dose Reduction

Dose Reduction Level	Oxaliplatin (mg/m^2)	Tegafur-Gimeracil-Oteracil Potassium (mg/dose)		
		$< 1.25\ m^2$	$\geq 1.25\ m^2$ to $< 1.5\ m^2$	$\geq 1.5\ m^2$
Initial dose	130	40	50	60
1-level reduction	100	25	40	50
2-level reduction	75	20	25	40
3-level reduction	50	Discontinued[a]		
4-level reduction	Discontinued	-		

[a] If tegafur-gimeracil-oteracil potassium combination drug is discontinued, oxaliplatin should also be discontinued.

7.3.4 Criteria for Oxaliplatin-Plus-Fluoropyrimidine Discontinuation

Except where specified below, both medications in the oxaliplatin-plus-fluropyrimidine chemotherapy regimen should be discontinued for any of the following reasons:

- Any Grade ≥ 4 peripheral neuropathy requires discontinuation of oxaliplatin.
- In case of persistent Grade 3 paraesthesia, oxaliplatin should be discontinued.
- Any Grade ≥ 3 mucocutaneous reaction possibly attributable to capecitabine, leucovorin, or tegafur-gimeracil-oteracil requires permanent discontinuation.
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding.
- Any drug-related liver function test abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5 to 10 × ULN for > 2 weeks
  - AST or ALT > 10 × ULN
  - Total bilirubin > 5 × ULN
  - Concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × ULN and total bilirubin > 2 × ULN

- Any oxaliplatin-related decrease in creatinine clearance to < 30 mL/min (using the Cockcroft Gault formula) requires discontinuation of oxaliplatin.
- Any drug-related AE that recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s) that was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE that the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- If any toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the participant might benefit from continuation of the component.

For toxicities that are not listed above, the treating investigators can decide to discontinue any individual chemotherapy agent, or all chemotherapy agents, if it is not the best interest in the participant per the local standards. If the fluoropyrimidine has to be discontinued completely, the benefit of continuing oxaliplatin should be carefully weighed against toxicity by the treating investigator per local standards.

Post-treatment study follow-up is critically important and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment will continue to be followed for collection of tumor surveillance assessments, safety [redacted] as per protocol.

7.3.5 Dose Delay Criteria for BMS-986213 or Nivolumab

BMS-986213 or nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation (see Section 7.3.7)
- All troponin elevations require a dose delay to allow for prompt cardiac evaluation
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication

Participants who require delay of BMS-986213 or nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume BMS-986213 or nivolumab dosing when the re-treatment criteria are met (see Section 7.3.6). If there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled.

7.3.6 Criteria to Resume BMS-986213 or Nivolumab Treatment

Participants may resume study treatments when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
  Note: Participants with combined Grade 2 AST and/or ALT AND total bilirubin values meeting discontinuation parameters (Section 7.3.7) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor/designee.
- Participants with drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement, may resume treatment after consultation with the BMS Medical Monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Troponin elevations will require the participant to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor/designee.

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol.

7.3.7 Criteria for BMS-986213 or Nivolumab Discontinuation

BMS-986213 or nivolumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation, regardless of control with hormone replacement.

  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 × ULN AND total bilirubin > 2 × ULN requires discontinuation

    *In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Grade 3 or higher myocarditis
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events that do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any event that leads to delay in dosing lasting > 8 weeks in the BMS-986213 or nivolumab PLUS FOLFOX treatment (or > 6 weeks in the BMS-986213 or nivolumab PLUS either XELOX or SOX treatment) from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks in the BMS-986213 or nivolumab PLUS FOLFOX treatment (or > 6 weeks in the BMS-986213 or nivolumab PLUS either XELOX or SOX treatment) from the previous dose that occur for nondrug-related reasons may be allowed if approved by the BMS medical monitor.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued BMS-986213 or nivolumab dosing.

Prior to reinitiating treatment in a participant with a dosing delay lasting > 8 weeks in the BMS-986213 or nivolumab PLUS FOLFOX treatment (or > 6 weeks in the BMS-986213 or nivolumab PLUS either XELOX or SOX treatment) from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

7.3.8 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[46] Participants treated with BMS-986213 or nivolumab in combination with chemotherapy will be permitted to continue their treatment beyond initial RECIST 1.1-defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional BMS-986213 or nivolumab treatment (alone or in combination with chemotherapy). All other elements of the main consent including description of reasonably foreseeable risks or discomforts or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with BMS-986213 or nivolumab.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive study evaluations according to Table 2-2 and Table 2-3. For the participants who continue treatment beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Investigational treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered nonmeasurable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

7.3.9 Management Algorithms for Immuno-Oncology Agents

IO agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Relatlimab and nivolumab are considered IO- agents in this protocol. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary (note for participants with dyspnea, CBC should be measured)
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

The above algorithms are found in Appendix 8 of this protocol.

7.3.10 Treatment of BMS-986213 and Nivolumab Infusion-related Reactions

Because both BMS-986213 (FDC relatlimab/nivolumab) and nivolumab contain only human Ig protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional BMS-986213 or nivolumab administrations

For Grade 2 symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or

acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study treatment. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.4 Preparation/Handling/Storage/Accountability of IP

For nivolumab, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

Similarly, for BMS-986213, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, and dispensing information.

The IPs should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IPs are only dispensed to study participants. The IPs must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatments are stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatments arise, do not dispense the study treatment and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Further guidance and information for final disposition of unused study treatments are provided in Appendix 2.

7.4.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.5 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as by recording capecitabine or S-1 administration in the participant drug diary (as applicable) , medical records, and electronic case report forms (eCRF). Participants should bring all drug (capecitabine or S-1) containers to each study visit for drug reconciliation. The drug diary should be submitted and reviewed at each clinic visit at the end of each cycle, as applicable. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance.

7.6 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the eCRF. All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the eCRF.

7.6.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.6.3)
- Any concurrent antineoplastic therapy (ie, chemotherapy [except those allowed per protocol], hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of GC/GEJ cancer)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Refer to the local institutional guidelines and/or the XELOX, SOX, and FOLFOX package inserts for possible prohibited and/or restricted treatments.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

7.6.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Participants who need anticoagulation treatment due to concomitant cardiovascular disease should be monitored closely; a maintenance of international normalized ratio (INR) > 2 is recommended.

Participants who are administered concomitantly fluoropyrimidine and oral coumadin-derivative anticoagulant therapy, such as warfarin, should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose. Participants who are administered capecitabine and other sensitive cytochrome p-450 (CYP) 2C9 substrate, or a CYP2C9 substrate with narrow therapeutic index, should be closely monitored for toxicity.

7.6.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.6.4 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and, if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

7.7 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986213 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the

study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases, BMS will follow local regulations

7.8 Blinding

This is a randomized, open-label study. Access to treatment codes will be restricted from all participants, and site and BMS personnel prior to primary database lock, with exceptions as specified below.

Treatment information is recorded on the CRF page and thus is accessible to all BMS personnel with access to the clinical database, as well as site staff and participants. This access will be used by Sponsor personnel such as GPVE, the MST, and the Medical Monitor to monitor safety of this novel combination in an unblinded manner as the study is ongoing, but not to perform unplanned efficacy analyses. Sponsor personnel may additionally receive access to randomization codes as assigned by IRT for purposes of interim analyses prescribed in the SAP or DMC charter. The unblinded access will not impact the integrity of the study as no early efficacy decisions will be made.

[redacted] A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) may obtain the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Documented radiographic PD per RECIST criteria, unless the participant meets criteria for treatment beyond progression
- Criteria listed in Sections 7.3.3.2, 7.3.3.3, 7.3.3.4, 7.3.4, and 7.3.7

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets 1 of the conditions outlined in Section 9.2.7 or if the investigator believes that it is in the best interest of the participant.

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5, Pregnancy.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8.1.1 Poststudy Treatment Study Follow-up

In this study, ORR is the primary endpoint of the study. Poststudy follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window (see Section 5). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including nonstudy required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study treatment-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, and fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Appendix 8.

For those participants receiving on-going treatment with BMS-986213 or nivolumab, troponin elevations will require the participant to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab for BICR. Sites should be qualified prior to scanning the first participant and understand the image acquisition guidelines and submission process as outlined in the CA224060 Imaging Manual to be provided by the imaging core lab.

Screening images should be acquired as outlined in Table 2-1. On study images should be acquired as outlined in Table 2-2, Table 2-3, and Table 2-4 from the date of randomization until participant has confirmed progression by BICR, subsequent therapy is started, withdraw of consent, or participant is lost to follow up.

Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and submitted to the BICR.

9.1.2 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging

time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments. It is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

MRI of brain without and with contrast should be acquired as outlined in Table 2-1, Table 2-2, Table 2-3, and Table 2-4. CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

Bone scans may be collected per local standards, as clinically indicated.

9.1.3 Imaging and Clinical Assessment

Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using RECIST 1.1 criteria. Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST 1.1 criteria. (See Appendix 5 for specifics

of RECIST 1.1 criteria to be utilized in this study.) A Best Overall Response of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

Tumor assessments for all participants should continue as per protocol even if dosing is delayed or discontinued. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

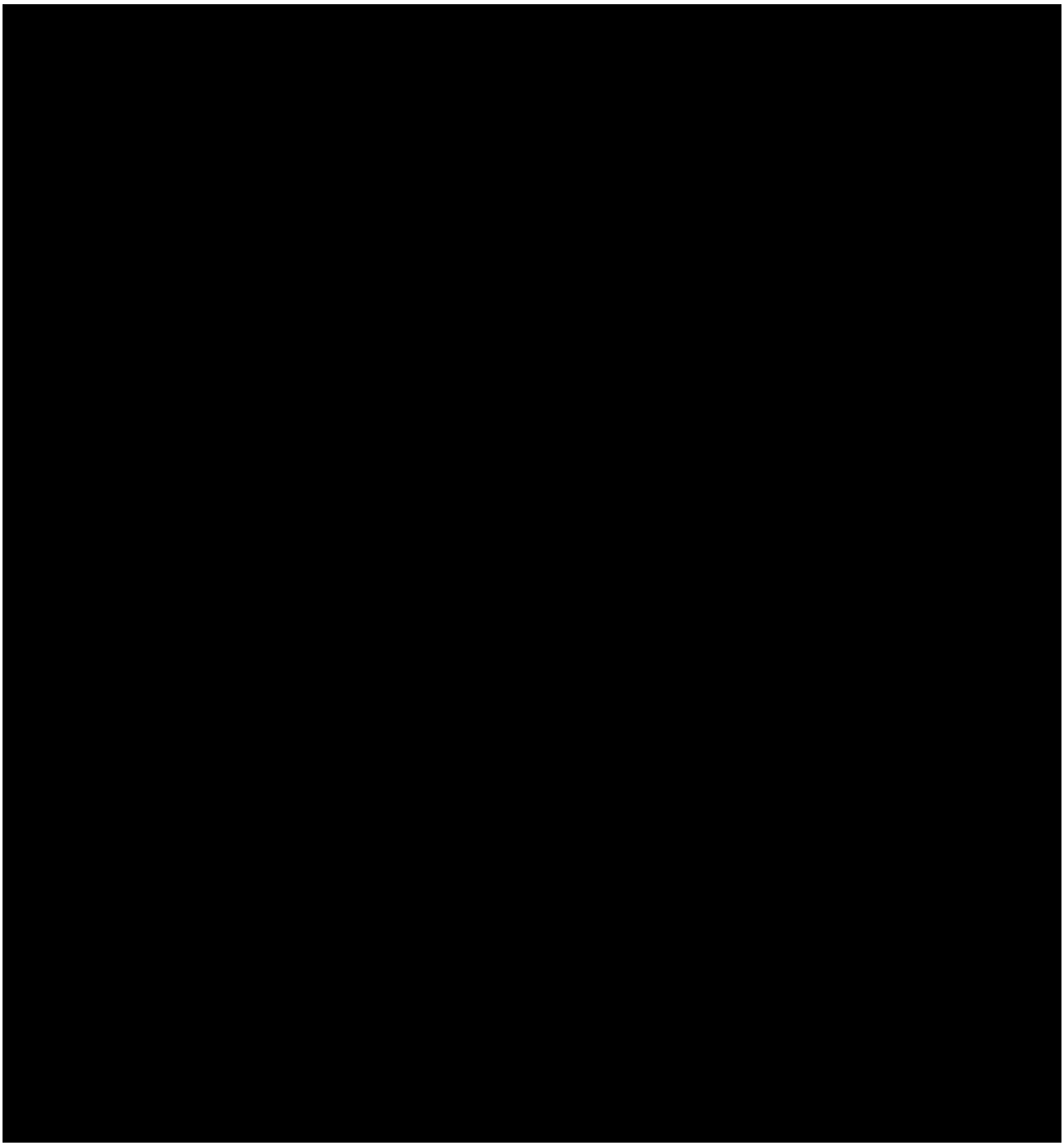
9.1.4 BICR Confirmation of Progression

Sites should submit all scans to the imaging core lab on a rolling basis, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be performed. The BICR review will be completed and the results provided to the site within 5 days of receipt of the scans, provided there are no pending imaging queries to the site.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2, until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.

[redacted]



9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Contacts for SAE reporting are specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochures (IBs) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing.

For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (e.g. a follow-up skin biopsy).

All nonserious AEs must be collected at the start of study treatment until the time points specified in the Schedule of Activities (Section 2).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when

collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected, unexpected serious adverse reaction is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least

5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Per Section 8.1, in most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or reinitiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/sponsor/ IRB/EC, as applicable.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (e.g. vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential DILI is defined as:

1) ALT or AST elevation > 3 × upper limit of normal (ULN)

   AND

2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, or any other potential safety assessment required or not required by protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

For this study, any dose of BMS-986213 or nivolumab greater than 160 mg/480 mg or 480 mg Q4W, or any dose of BMS-986213 or nivolumab greater than 120 mg/360 mg or 360 mg Q3W, respectively, within a 24 hour time period will be considered an overdose.

In the event of an overdose the investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. Safety assessments include AEs, physical examinations, vital signs, performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities (see Section 2).

9.4.2 Vital Signs

Refer to Schedule of Activities (see Section 2).

9.4.3 Electrocardiograms

Refer to Schedule of Activities (see Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Laboratory assessments are listed in Table 9.4.4-1.

- Investigators must document their review of each laboratory safety report
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2)

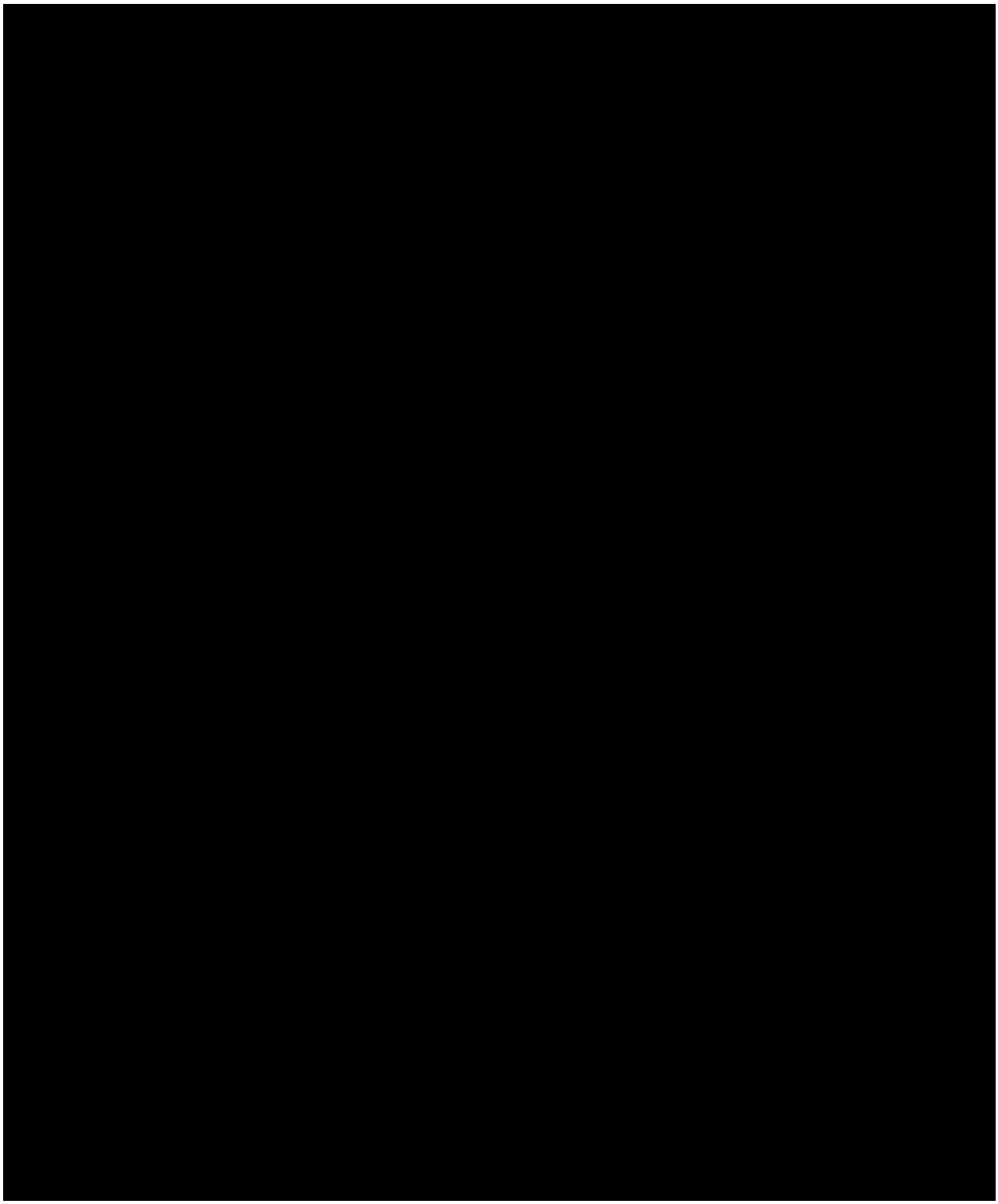
Table 9.4.4-1: Laboratory Assessment Panels

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase	Albumin
Alanine aminotransferase	Sodium
Total bilirubin	Potassium
Alkaline phosphatase	Chloride
Gamma-glutamyl transferase only when alkaline phosphatase is ≥ Grade 2	Calcium
	Phosphorus
Creatinine	Magnesium
Blood urea nitrogen or serum urea level	TSH, free T3 and free T4 **- screening only**
Glucose	TSH, with reflexive free T3 and free T4 if TSH is abnormal **- on treatment**
Direct bilirubin	
Lactate dehydrogenase	Creatinine clearance - **screening only**
Uric acid	FSH (if needed to document postmenopausal status as defined in Appendix 4) **- screening only**
Troponin (local standard to be used/allowed)	
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
Ph	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology (at screening)	
hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen, , HIV antibodies. (Testing for HIV must be performed at sites where mandated by local requirements, see Appendix 7)	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening only; required to confirm menopause in women < age 55)	

Abbreviations: HIV = human immunodeficiency virus; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

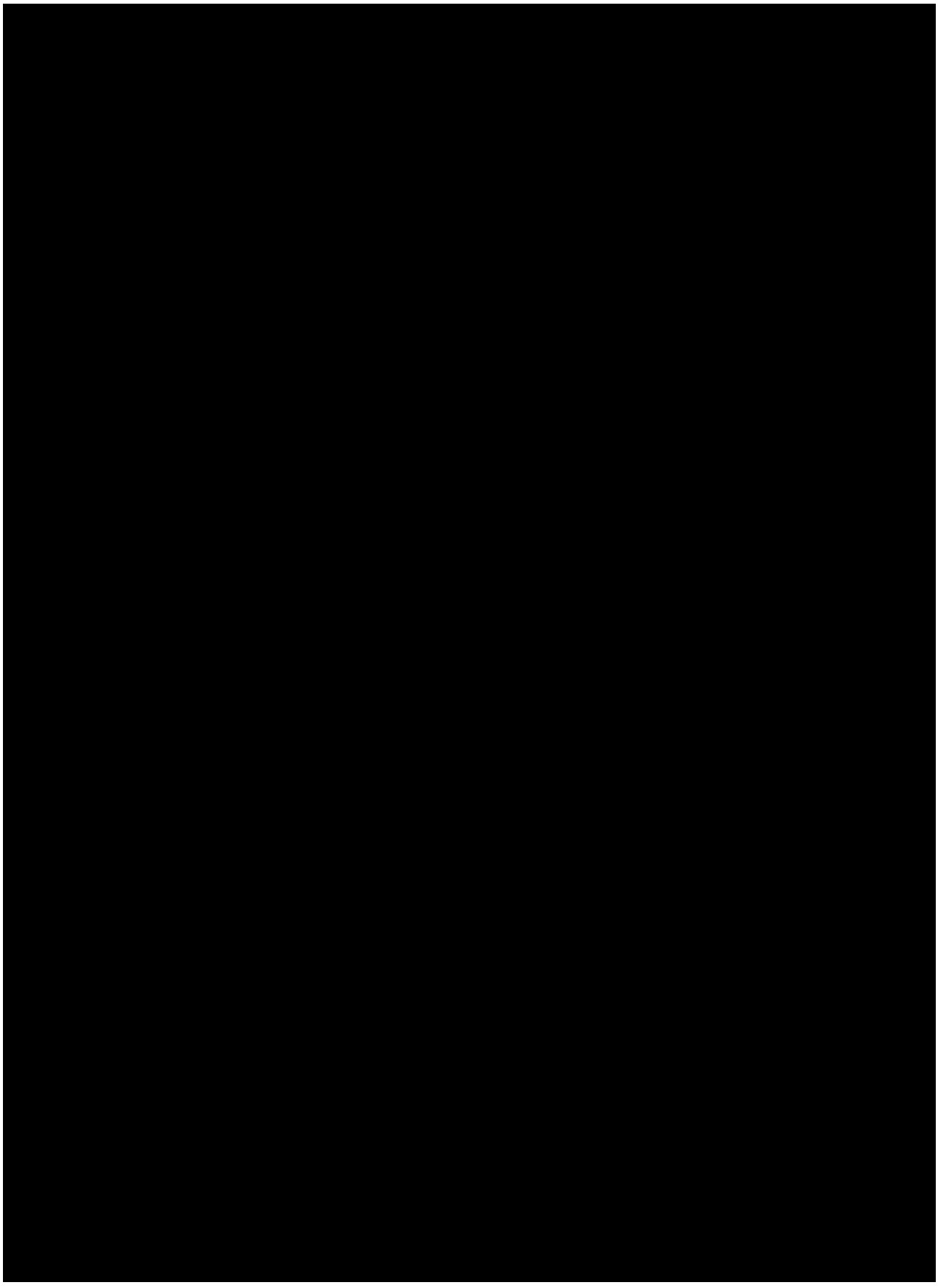
9.4.5 Imaging Safety Assessment

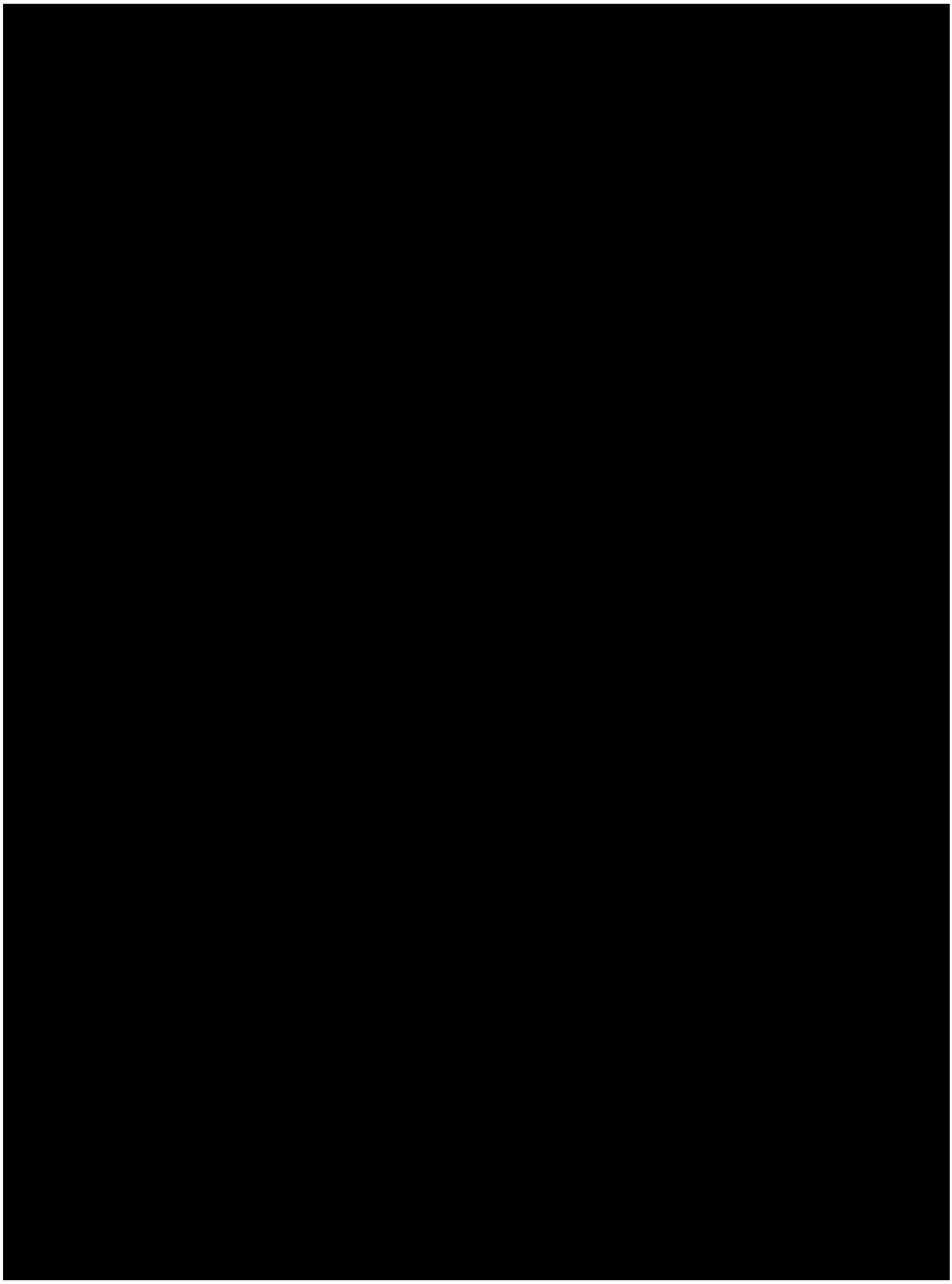
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.



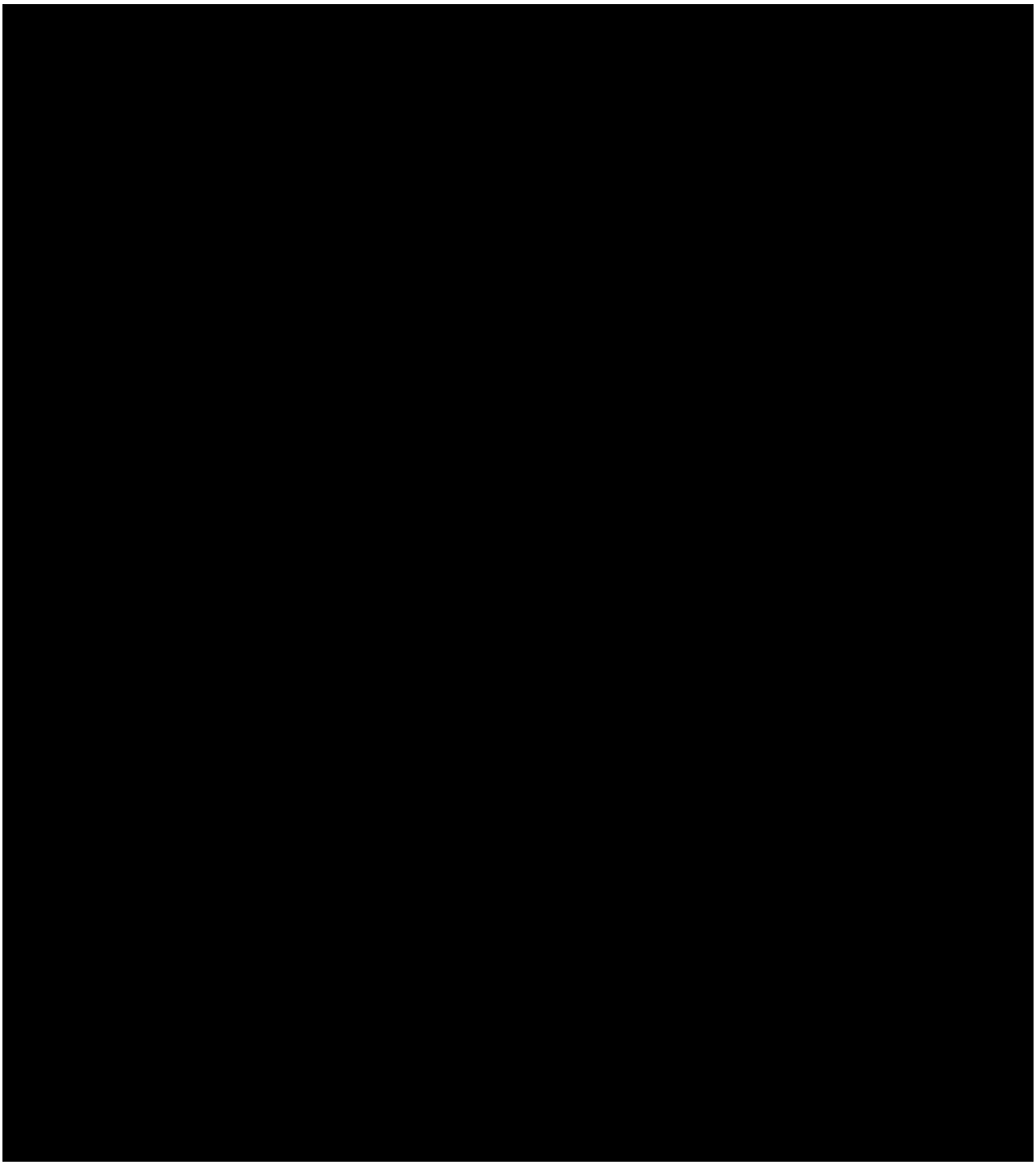
[redacted]

[redacted]

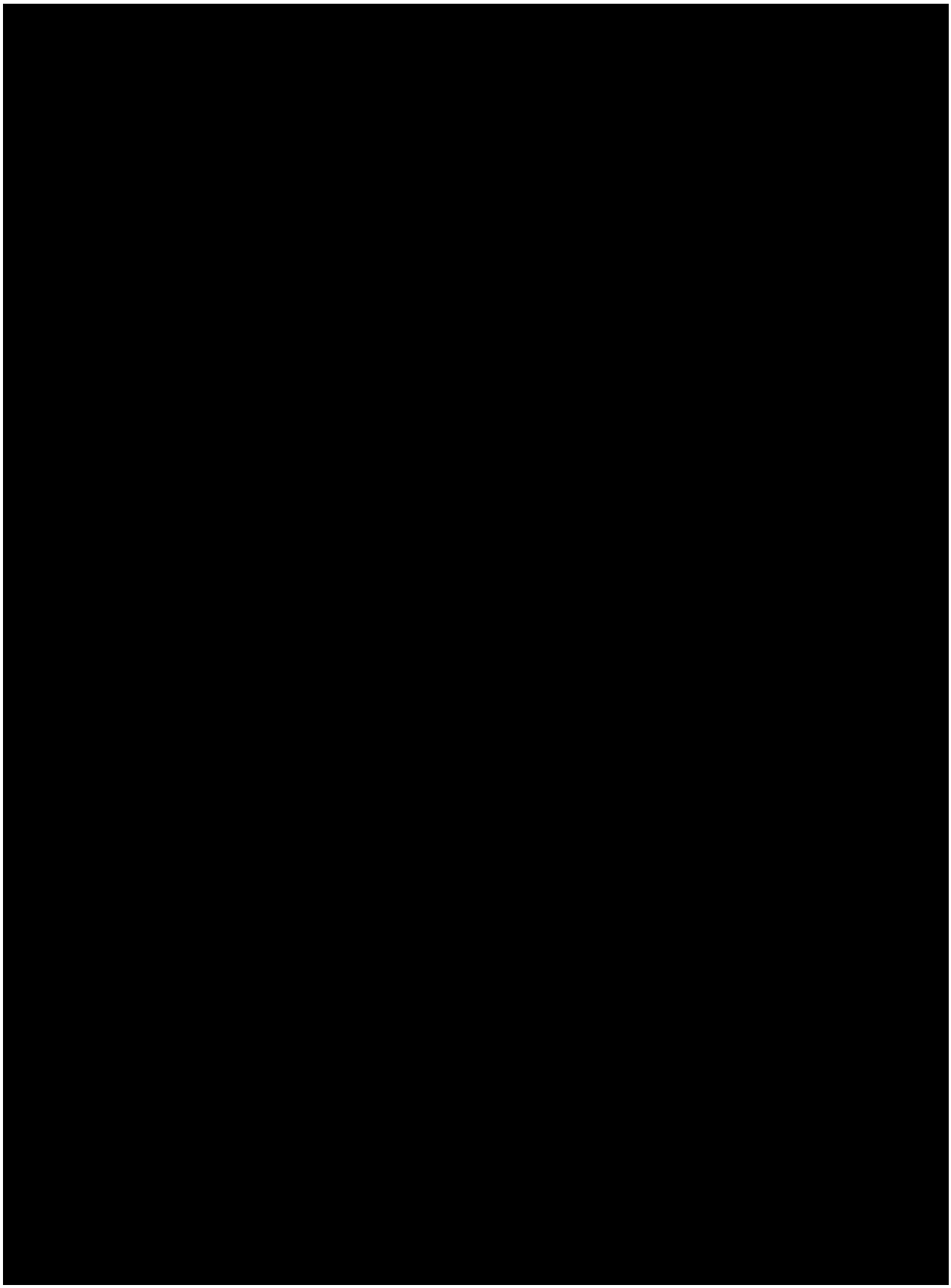




[redacted]



[redacted]



[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the study is based on the primary objective, ie, on the comparison of the ORR of participants who were randomized to receive BMS-986213 in combination with chemotherapy versus those randomized to receive nivolumab and chemotherapy and with LAG-3 positive expression. A total of approximately 250 participants are expected to be randomized in a 1:1 ratio to the relatlimab+nivolumab+chemotherapy, or nivolumab+chemotherapy arms. [redacted] In order to ensure sufficient follow-up to achieve objective response and to assess the durability of response, the last

patient last visit for the ORR analysis will occur after the last (response evaluable) patient randomized had the chance to proceed with the Week 24 tumor assessment.

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined below:

Population	Description
Enrolled	All participants who sign an informed consent form. This is the dataset for disposition (and select safety)
Randomized participants	All participants who are randomized to any treatment. This is the dataset for baseline demographics and select efficacy analyses.
LAG-3 positive participants	All randomized participants in the LAG-3 positive group. This is the dataset for baseline demographics and primary efficacy analyses.
Response evaluable participants	All randomized participants who had measurable lesions at baseline

[redacted]

Population	Description
Treated participants	All randomized participants who take at least 1 dose of study treatment. This is the dataset for safety analyses.

10.3 Statistical Analyses

A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm as randomized overall and by LAG-3 expression group using descriptive statistics.

10.3.2 Efficacy Analyses

Primary Endpoint	Statistical Analysis Methods
• Objective response rate (ORR) as assessed by BICR in participants who are LAG-3 positive is defined as the number of participants with a best overall response (BOR) of CR or PR divided by the number of randomized participants who are LAG-3 positive in each arm. BOR is defined as the best response designation based on the BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by the investigator) or death, or the date of subsequent anti-cancer therapy, whichever occurs first.	• ORR as assessed by BICR in participants who are LAG-3 positive will be compared between the BMS-986213 in combination with chemotherapy and nivolumab in combination with chemotherapy using a two-sided Cochran-Mantel-Haenszel test stratified by region (J/T or ROW) and PD-L1 status (CPS < 1 or indeterminate, CPS ≥ 1 to <5, CPS ≥ 5) as recorded in the IRT. Associated 70% CIs for ORR difference will be calculated. Additionally, ORR along with the exact 95% CI for each arm will be calculated using the Clopper-Pearson method.[52]
Secondary	
• Objective Response Rate (ORR) as assessed by investigator in participants who are LAG-3 positive is defined as the number of participants with a best overall response (BOR) of CR or PR divided by the number of randomized participants who are LAG-3 positive in each arm. BOR is defined as the best response designation based on the investigator, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1) or the date of subsequent anti-cancer therapy, whichever occurs first.	• ORR based on investigator in LAG-3 positive population will be compared between the BMS-986213 in combination with chemotherapy vs Nivolumab in combination with chemotherapy using a two-sided Cochran-Mantel-Haenszel test stratified by region (J/T ROW) and PD-L1 status as recorded in the IRT. Additionally, ORR along with the exact 95% CI for each arm will be calculated using the Clopper-Pearson method.[52]

Primary Endpoint	Statistical Analysis Methods
• Duration of Response (DOR) (as assessed by BICR and as assessed by investigator) in participants who are LAG-3 positive, is defined as the time between the date of first documented response (CR or PR) to the date of the first PD, per RECIST 1.1 or death due to any cause, whichever occurs first. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death.	• Summary of DOR with median (95% CI) and range (minimum, maximum) by K-M method. Participants who did not have documented PD per BICR or investigator per RECIST 1.1 criteria and who did not die, will be censored at the date of the last evaluable tumor assessment on or prior to initiation of subsequent anti-cancer therapy. Participants who did not have any on-study tumor assessments and did not die (or died after initiation of subsequent anti-cancer therapy) will be censored at the randomization date. Those who started any subsequent anti-cancer therapy without a prior reported PD per BICR or investigator will be censored at the last tumor assessment prior to or on the initiation of the subsequent anti-cancer therapy
• ORR in participants who are LAG-3 negative and in the population overall (as assessed by BICR and by investigator) is defined as the number of participants with a best overall response (BOR) of CR or PR divided by the number of randomized participants with LAG-3 negative cancers or participants in the overall population in each arm	• ORR in participants who are LAG-3 negative and in the population overall as assessed by BICR and investigator will be compared between the BMS-986213 in combination with chemotherapy and Nivolumab in combination with chemotherapy arms using a two-sided Cochran-Mantel-Haenszel test stratified by region (J/T or ROW) and PD-L1 status (CPS < 1 or indeterminate, CPS ≥ 1 to <5, CPS ≥ 5) as recorded in the IRT. Additionally, ORR along with the exact 95% CI for each arm will be calculated using the Clopper-Pearson method.[52]
• DOR in participants who are LAG-3 negative and DOR in the overall population (as assessed by BICR and as assessed by investigator) is defined as the time between the date of first documented response (CR or PR) to the date of the first PD, per RECIST 1.1 or death due to any cause, whichever occurs first. • Overall survival time (OS) in participants who are LAG-3 positive or LAG-3 negative separately and overall, is defined as the time between the date of randomization and the date of death due to any cause. For those without documentation of death, OS will be censored on the last date the participant was known to be alive.	• Summary of DOR in the LAG-3 negative and in the overall populations with median (95% CI) and range (minimum, maximum) by K-M method. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. In addition the censoring rules apply as in the LAG-3 positive group, described above. • OS: The difference in the distribution of OS will be assessed between BMS-986213 in combination with chemotherapy vs nivolumab in combination with chemotherapy separately in participants who are LAG-3 positive and LAG-3 negative using a two-sided log rank test and a significance level of 15% one-sided (30% 2-sided), stratified by region (Japan/Taiwan [J/T] or Rest of World [ROW]) and PD-L1 expression status as recorded in the IRT. For this comparison, the HR with its associated two-sided 70% confidence intervals (CI) will be estimated via a stratified Cox model with randomized treatment arm as the only covariate in the model. OS for each treatment arm will be estimated and plotted using the Kaplan-Meier (K-M) product-limit method. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survival function. The analysis will be repeated to assess OS differences between the 2 arms across all participants, using the same methods as above with an additional stratification factor of LAG-3 expression

Primary Endpoint	Statistical Analysis Methods
• PFS in participants who are LAG-3-positive, LAG-3 negative, and overall, as assessed by a Blinded Independent Central Review (BICR), using RECIST 1.1. PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first. Participants who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death.	• PFS: The difference in the distribution of PFS between BMS-986213 in combination with chemotherapy vs Nivolumab in combination with chemotherapy will be assessed separately in participants who are LAG-3 positive and LAG-3 negative via a two-sided, log-rank test and a significance level of 15% one-sided (30% 2-sided), stratified by the same factors as above. The hazard ratio and the corresponding 70% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each randomized arm will be estimated and plotted using the K-M product limit method. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for PFS. The above analysis will be repeated to assess PFS differences between the 2 arms across all participants, using the same methods as above with an additional stratification factor of LAG-3 expression. The same censoring rules apply as for DOR.
[redacted]	

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; [redacted] GC = gastric cancer; GEJ = gastroesophageal junction; J = Japan; K = Korea; K-M = Kaplan-Meier; ORR = objective response rate; OS = overall survival; [redacted] PD = disease progression; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; [redacted] PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; ROW = rest of world; T = Taiwan.

10.3.3 Safety Analyses

All safety analyses will be performed on the Safety Sample.

Endpoint	Statistical Analysis Methods
Secondary • The Safety and tolerability objective will be measured by the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, deaths, and laboratory abnormalities in each arm by LAG-3 group and overall	• Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 5.0 criteria.

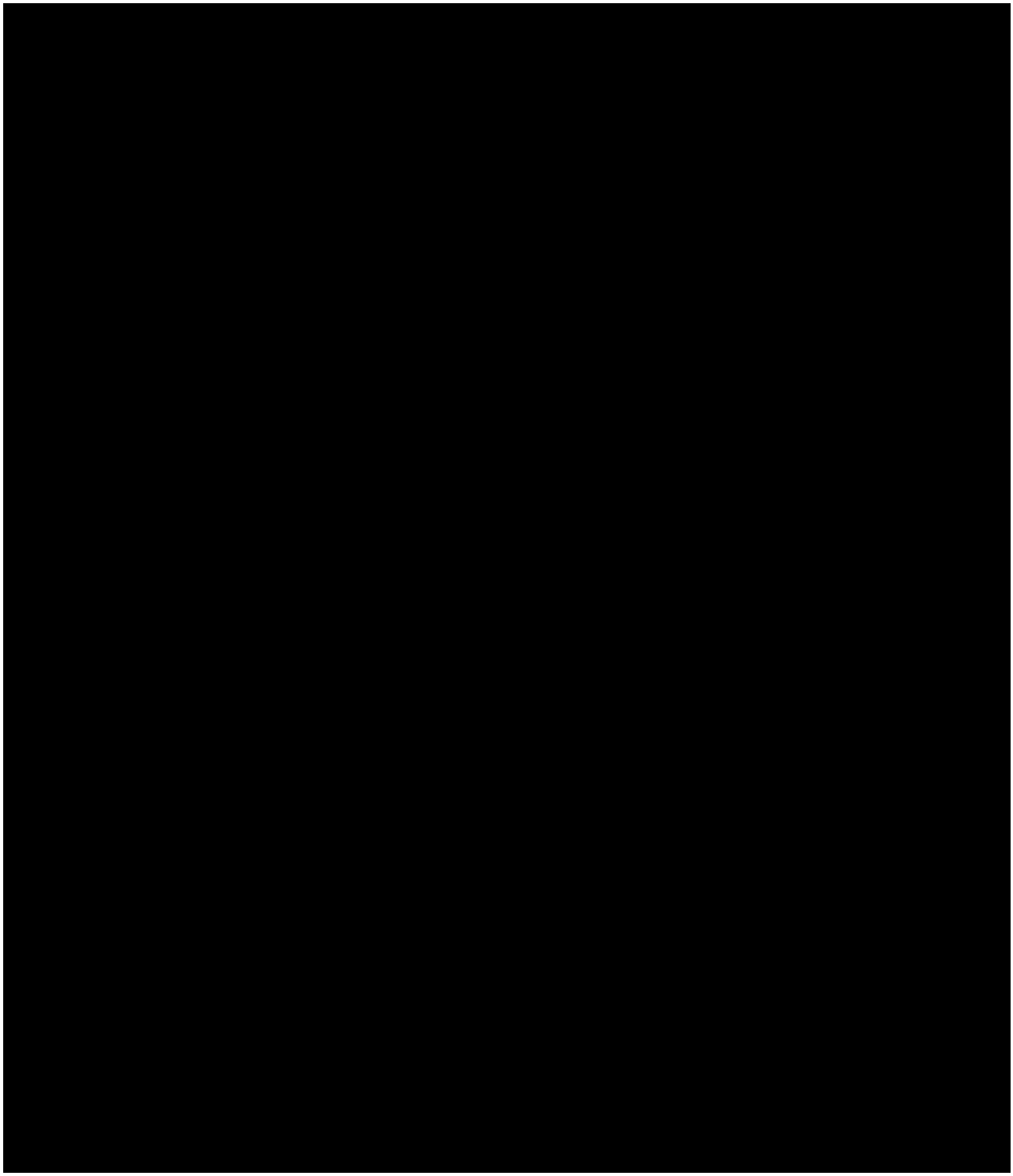
[redacted]

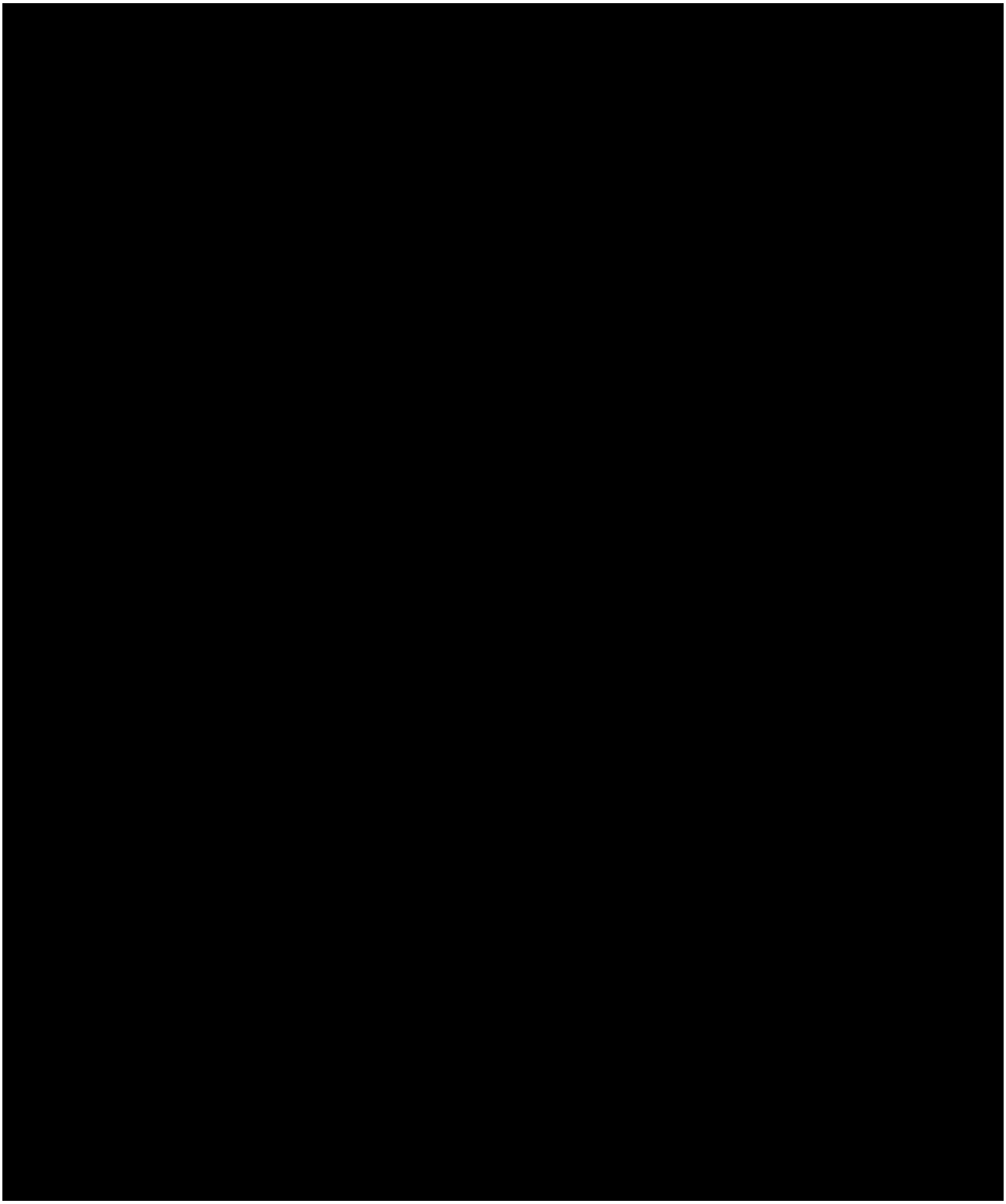
10.3.9 Interim Analyses

There are no official planned interim analyses. Approximately after at least 24 weeks since the last participants has been randomized, or after all randomized participants had an opportunity to complete at least 24-week scans, the ORR analysis will be performed. Additional analyses that allow for longer follow-up to estimate the DOR and other time to event endpoints will also be performed, after at least 9 months since the last participant has been randomized. In addition planned analyses will be produced for DMC evaluation of risk/benefit, as per the DMC charter.

11 REFERENCES

1 Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 2007;8(3):239-45.





[redacted]

[redacted]

46 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

[redacted]

52 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.

[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
5-FU	5-fluorouracil
[redacted]	
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BSA	body surface area
[redacted]	
C	Celsius or Cycle
[redacted]	
CFR	Code of Federal Regulations
CI	confidence interval
cm	centimeter
[redacted]	
CNS	central nervous system
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
[redacted]	
CTLA 4	cytotoxic t-lymphocyte-associated antigen 4

Term	Definition
[redacted]	
CYP	cytochrome p-450
D	day
DCR	disease Control Rate
DILI	drug induced liver injury
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
[redacted]	
DOR	duration of response
[redacted]	
ECG	electrocardiogram
[redacted]	
ECOG	Eastern Cooperative Oncology Group
eg	exempli gratia (for example)
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
[redacted]	
FDA	Food and Drug Administration
FDC	fixed dose combination
FFPE	formalin-fixed, paraffin-embedded
[redacted]	
FOLFOX	oxaliplatin, leucovorin, and fluorouracil
FSH	follicle stimulating hormone
FU	follow-up
GEJ	gastroesophageal junction
GC	gastric cancer

Term	Definition
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
[redacted]	
HR	hazard ratio
[redacted]	
IA	interim analysis
IB	Investigator's Brochure
[redacted]	
IEC	Independent Ethics Committee
[redacted]	
Ig	immunoglobulin
IMAE	immune-mediated adverse events
INR	international normalized ratio
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
J	Japan
K	Korea
kg	kilogram
K-M	Kaplan-Meier
L	liter
LAG-3	lymphocyte activation gene 3

Term	Definition
[redacted]	
mg	milligram
MHC	major histocompatibility complex
min	minute
mL	milliliter
mAbs	monoclonal antibodies
MI	myocardial infarction
[redacted]	
MRI	magnetic resonance imaging
[redacted]	
□g	microgram
[redacted]	
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[redacted]	
ORR	objective response rate
OS	overall survival
[redacted]	
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
[redacted]	

Term	Definition
[redacted]	
PR	partial response
[redacted]	
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
[redacted]	
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
[redacted]	
ROW	rest of world
SAE	serious adverse event
SD	stable disease
SI	International System of Units
[redacted]	
SOX	S1 and oxaliplatin
T	Taiwan
T3	triiodothyronine
T4	thyroxine
[redacted]	
TnI	troponin I
TnT	troponin T
[redacted]	
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WOCBP	women of childbearing potential

Term	Definition
XELOX	capecitabine and oxaliplatin

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of 1 or more participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to participants and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participants' signed ICF and, in the US, the participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on-site.

It is however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any

principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 24 weeks after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 33 weeks after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 33 weeks after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 33 weeks after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 33 weeks after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [redacted].[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

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

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for

unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the

date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCE

[1] 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: 228-47.

APPENDIX 6 ECOG STATUS SCALE

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	**Description**
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of alight or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

APPENDIX 7 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Italy, Spain, Peru and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 3j	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 8 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

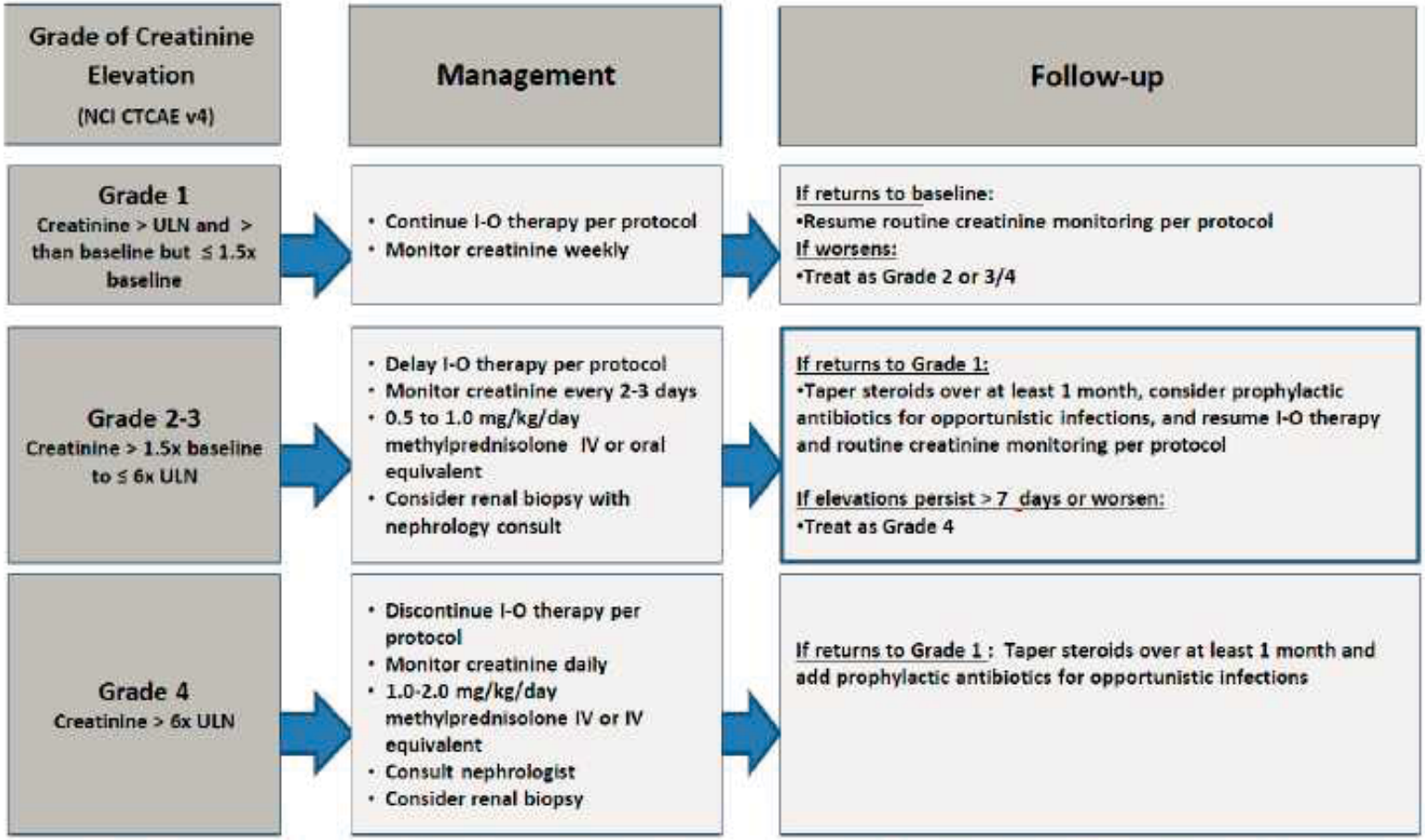
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

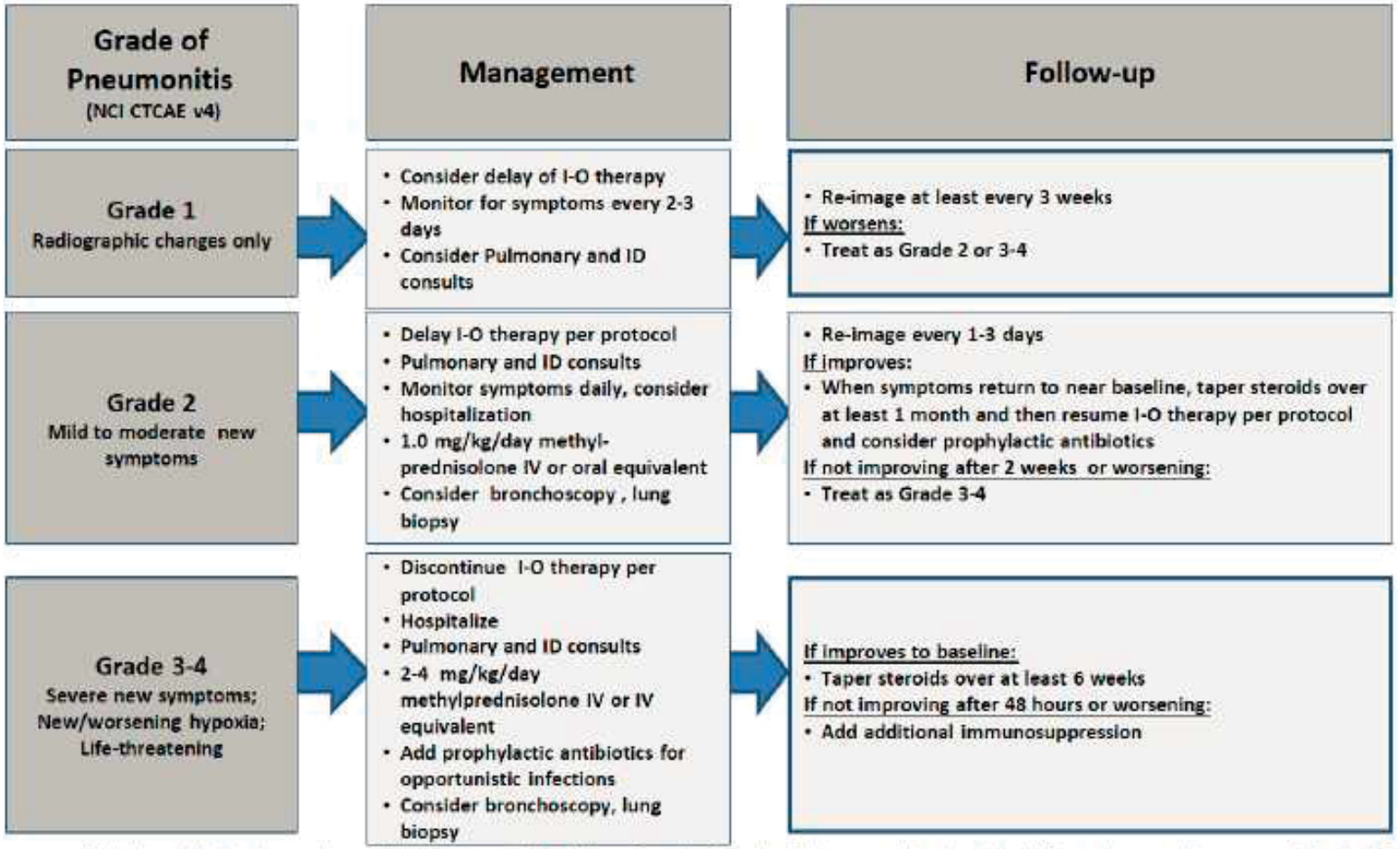


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

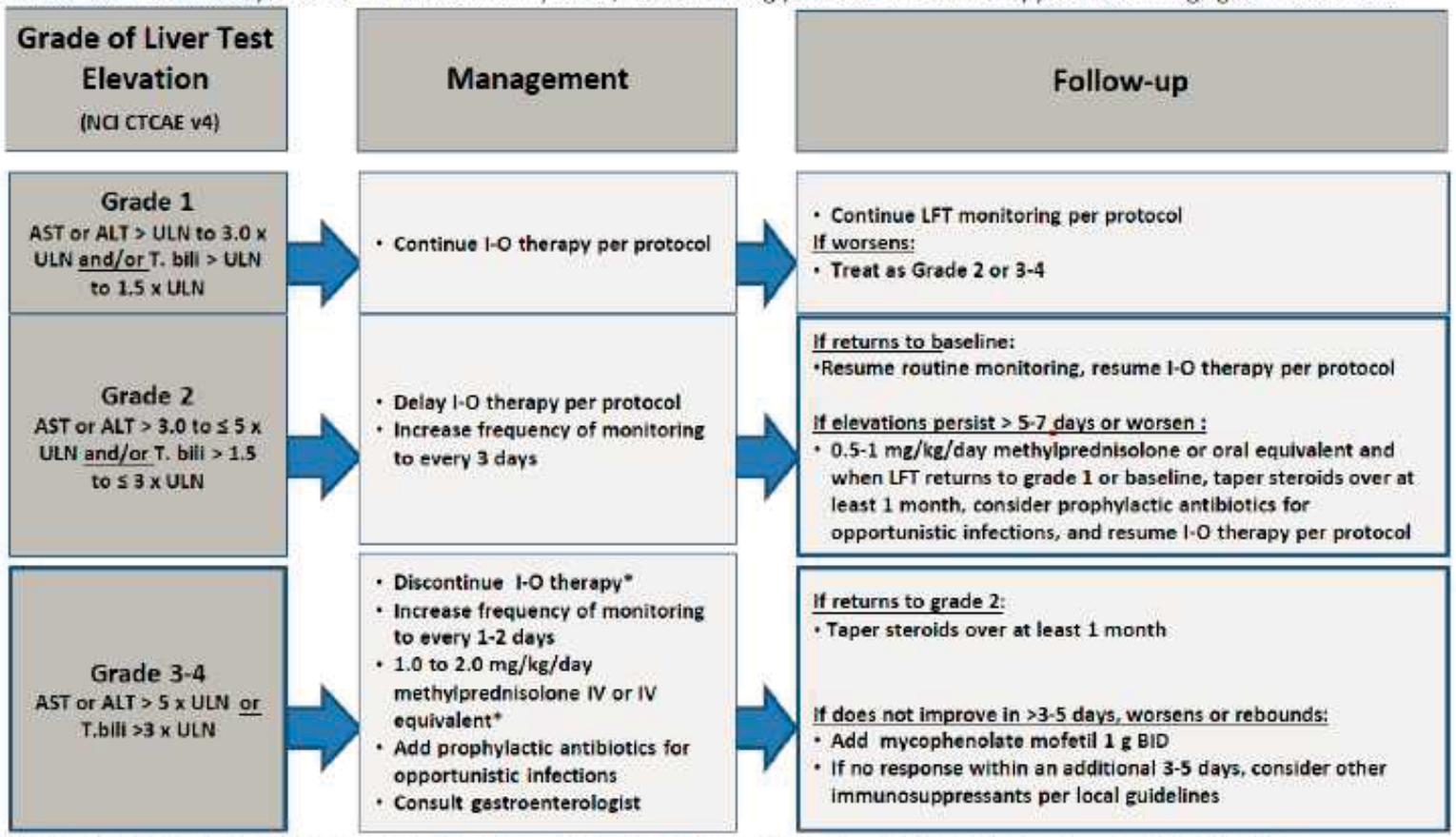


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2018

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



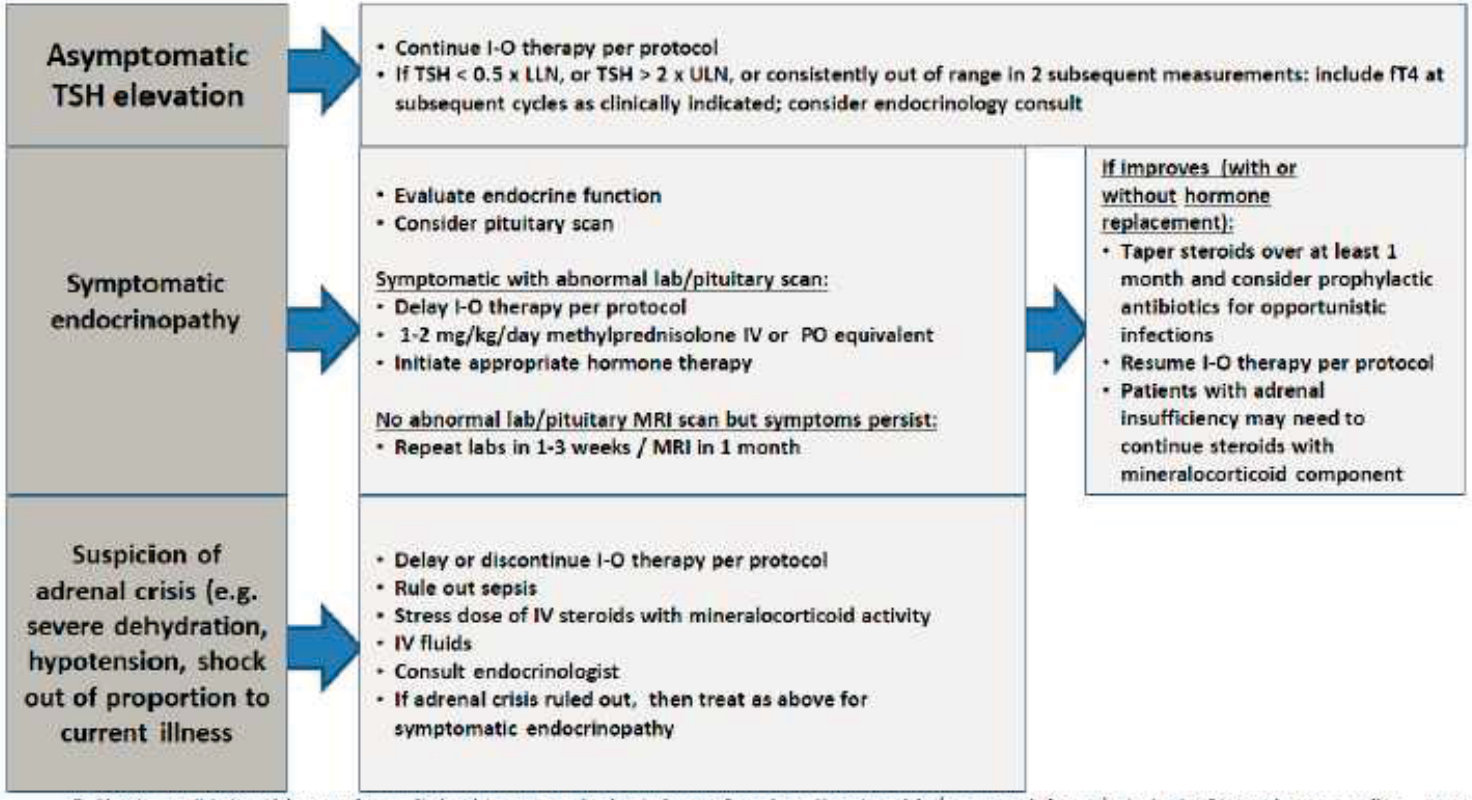
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

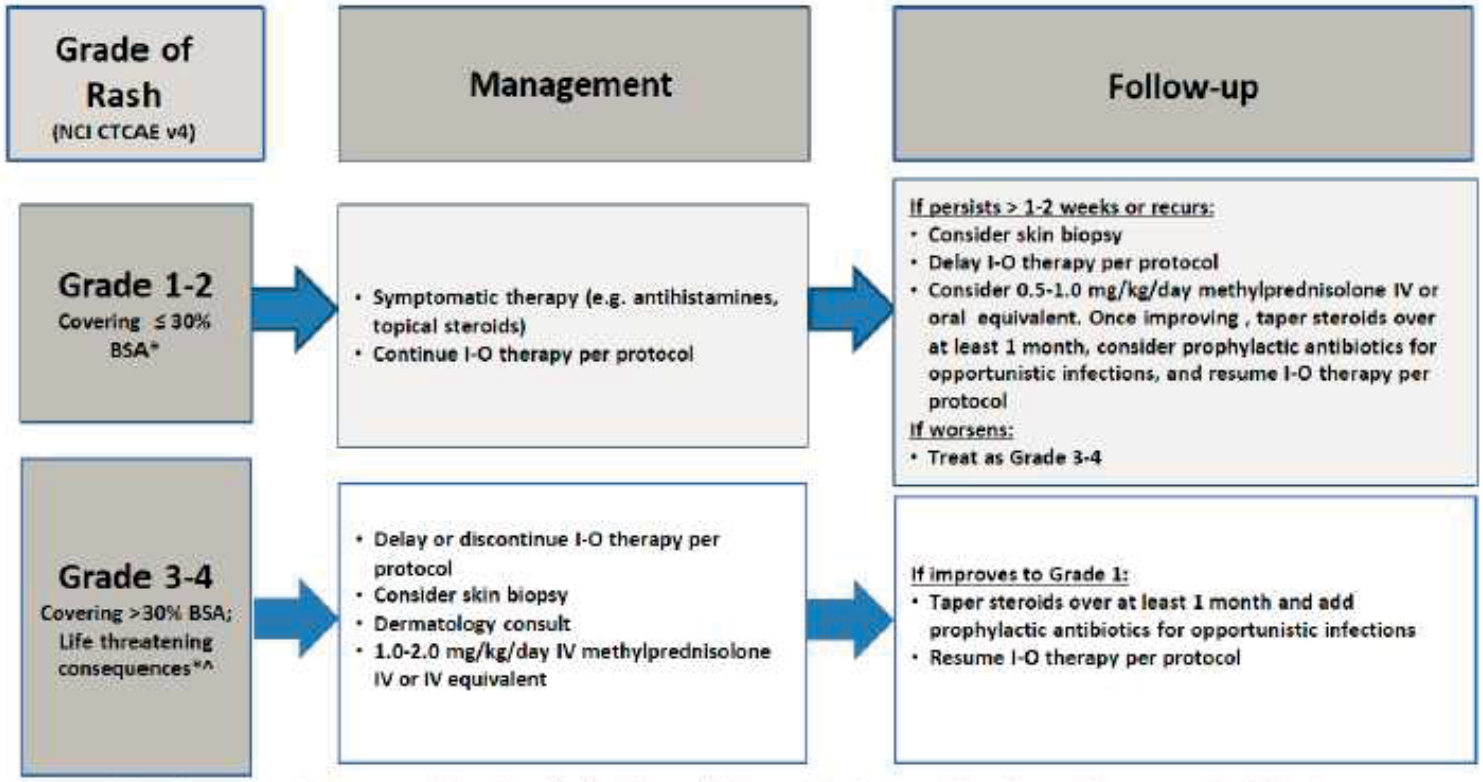
Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2018

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2018

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Event	Management	Follow-up
Asymptomatic Troponin Elevation	• Delay I-O therapy • Repeat and monitor troponin • Consider cardiology consultation with diagnostic workup; ECG, echocardiogram, cardiac MRI per recommendation of cardiologist • Consider corticosteroids per treating physician	• Monitor troponin until recovery • Resume I-O therapy upon recovery

Grade 2 Myocarditis
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3-4 Myocarditis
Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac care unit with heart failure therapy as indicated
	• Cardiac evaluation to include:
	  ○ Troponin and BNP monitoring
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in cardiac transplant and/or cardiac complications of immunotherapy
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; I-O = immuno-oncology; IV = intravenous; MRI = magnetic resonance imaging

APPENDIX 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 02, 16-Nov-2018

To [redacted] include updates to reflect current data and protocol standards, and make administrative corrections.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Added text reflecting addition of Data Monitoring Committee.	BMS development decision
Table 2-1 Screening Assessments - All Participants (CA224060)	Added language providing for the optional collection of tumor tissue older than 3 month	Revision to Translational Medicine scope of investigation
3.3 Benefit/Risk Assessment	Revised text and added text reflecting addition of updated safety data and Data Monitoring Committee.	Reflects updated data
5.1.1 Screening Phase	Removed language requiring an associated pathology report to accompany FFPE tissue block or unstained tumor tissue section for biomarker evaluation prior to randomization; pathology report is optional. Added language providing for the optional collection of tumor tissue older than 3 months	Administrative correction Revision to Translational Medicine scope of investigation
5.1.5 Data Monitoring Committee	Added section defining use of Data Monitoring Committee.	BMS development decision
[redacted]		
6.1 Inclusion Criteria	Removed language requiring an associated pathology report to accompany FFPE tissue block or	Administrative correction

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	unstained tumor tissue section for biomarker evaluation prior to randomization; pathology report is optional.	
6.2 Exclusion Criteria	Revised language excluding participants who received live/attenuated vaccines within 30 days of first treatment Removed exclusion of recombinant human erythropoietin within 3 weeks of first study drug administration	Reflects new required content Administrative correction
7.2 Method of Treatment Assignment	Added text regarding treatment access rules	Procedural clarification
7.3.9 Management Algorithms for Immuno-Oncology Agents	Added "Myocarditis" to list of available algorithms for guidance on management and treatment of myocarditis	To meet current standards
7.6.1 Prohibited and/or Restricted Treatments	Added prohibition of any live/attenuated vaccine during treatment up to 100 days post treatment	To meet current standards
9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Removal of prescreening consent option	Administrative correction
[redacted]		

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
10.3.9 Interim Analyses	Revised text to incorporate analyses for DMC evaluation of risk/benefit	BMS development decision
Appendix 3	Updated definitions and procedures for recording, evaluating, follow-up and reporting AEs and SAEs	To meet current standards
Appendix 8	Added "Myocarditis" to list of available algorithms for guidance on management and treatment of myocarditis	To meet current standards
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 29-Jun-2018

The primary purpose for this revision was to update Appendix 4, WOCBP to current standards, and to modify the PD-L1 stratification levels.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Modified PD-L1 stratification levels for statistical analyses	Due to a change in methodology and evolving understanding of the relevant cutoffs for the gastric population
[redacted]		

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria	Additional exclusion criterion added	[redacted]
Section 8.1 Discontinuation from Study Treatment	Modified text to include consideration by the investigator of abnormal liver tests for participant discontinuation, and revision of procedures to follow in case of pregnancy	To meet current standards
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Modified text regarding collection of AE and SAE information	To meet current standards
[redacted]		
Appendix 4	Updated appendix for WOCBP	To meet current standards
All	Updated CTCAE to version 5	To meet current standards
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized