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): Jul 27, 2020

CSR STATISTICAL ANALYSIS PLAN

AN OPEN LABEL STUDY OF RELATLIMAB AND NIVOLUMAB WITH CHEMOTHERAPY VERSUS NIVOLUMAB WITH CHEMOTHERAPY IN PATIENTS WITH GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

Protocol CA224060

VERSION # 2.0

DATE: 27-JUL-2020

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1 BACKGROUND [redacted]

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 subjects with unresectable, untreated, 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 anti-tumor 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).

Research Hypothesis:

In subjects with untreated, unresectable, locally advanced or metastatic gastric cancer (GC) or gastroesophageal junction (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.

Schedule of Analyses:

ORR is the primary endpoint for this study. The primary ORR analysis will be performed once all randomized subjects have had the potential for 6 months of follow-up. Additional analyses will be performed to evaluate the duration of response e.g. once everyone has 9 months of follow-up.

An independent Data Monitoring Committee (DMC) will monitor periodic interim safety and efficacy reports to allow for a risk/benefit assessment. An initial safety evaluation will be conducted (by the DMC) when the first 20 subjects randomized in the study have received at least one dose and have a minimum of 6 weeks follow-up.

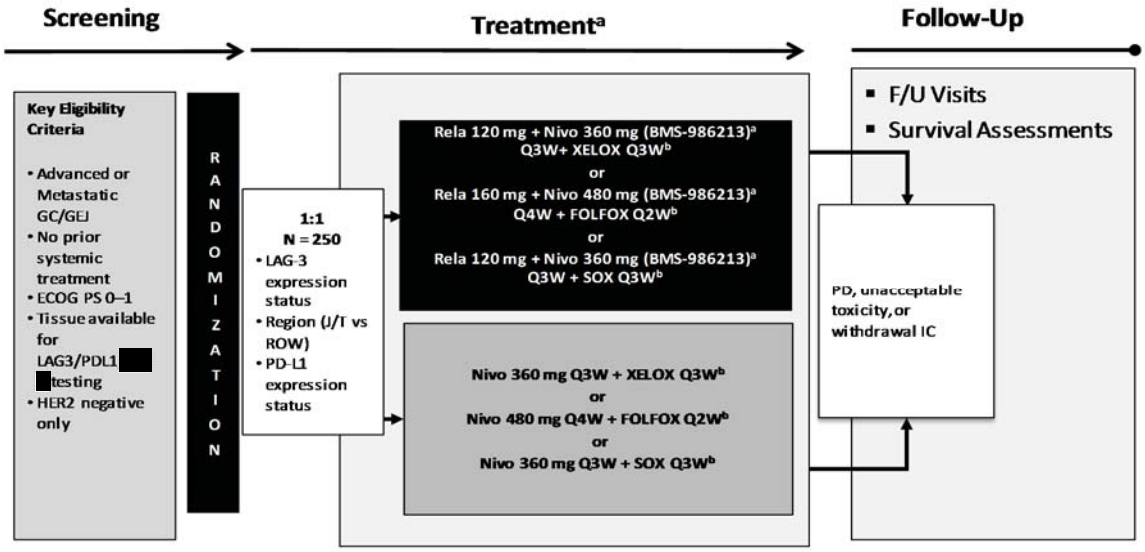
2 STUDY DESCRIPTION

2.1 Study Design

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

[redacted]

Figure 2.1-1: 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

Screening Phase

- The Screening Phase begins by establishing the participant's initial eligibility and signing of the informed consent form.
- Subjects are enrolled using the Interactive Response Technology (IRT) system.
- A pre-treatment tumor sample is required to be submitted from all subjects. 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 ≥5%, CPS ≥ 1 to <5, or CPS < 1% (including indeterminate)). LAG-3 expression status and PD-L1 CPS must be determined by the central lab prior to completion of the remaining screening procedures.

Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization

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

- Subjects 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), unacceptable toxicity, or participant withdrawal of consent, whichever comes first
- Stratification factors for this study are:
  - LAG-3 expression (≥1% or <1%; no indeterminate allowed)
  - PD-L1 CPS expression status (≥5%, ≥ 1 to <5, or < 1% (including indeterminate))

[redacted]

Note: region (Japan/Taiwan [J/T] vs Rest of world [ROW]) was originally a stratification factor for the study and is in the IRT system, but no one from Japan/Taiwan enrolled in the study. Therefore, although it is still in the system as a stratification factor for the study, it will not be analyzed nor used as such.

- 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 exceptions identified in the protocol:
  - BMS-986213 or nivolumab is allowed to be administrated 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
  - Subjects assigned to FOLFOX will have only FOLFOX administered on Day 15 of the odd numbered cycles (i.e. Cycles 1, 3, 5, etc.) and Day 1 and 29 of the even numbered cycles (i.e. 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 (i.e., PD, unacceptable toxicity, or participant withdrawal of consent)

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 (±7days) 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.

Any additional follow-up data collected up to 135 days since last dosing (in select sites) will be presented in listings.

2.2 Treatment Assignment

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, subjects 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 ≥5%, CPS ≥ 1 to <5, or CPS < 1% or including indeterminate) provided by the central lab directly to the IRT system
- Anatomical location (gastric vs GEJ)
- 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) and PD-L1
- CPS expression status ((≥5%, ≥ 1 to <5, or < 1% (including indeterminate)). The exact procedures for using the IRT will be detailed in the IRT manual.

  Note: region (Japan/Taiwan [J/T] vs rest of world [ROW]) was originally a stratification factor for the study, but no one from Japan/Taiwan enrolled in the study. Therefore, although it is still in the system as a stratification factor for the study, it will not be analyzed nor used as such.

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

- Subjects 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/m2 administered IV on Days 1 and 22 of each treatment cycle every 6 weeks, and capecitabine 1000 mg/m2 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.
- Subjects 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 Cycle (Cycle 1, 3, 5, etc.) and Day 15 of every even numbered 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.
- Subjects 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/m2 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/m2/dose): BSA <1.25 m2, 40 mg/dose; ≥1.25 and <1.5 m2, 50 mg/dose; ≥1.5 m2, 60 mg/dose.

2.3 Blinding and Unblinding

This is a randomized, open-label study. 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 subjects. 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) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

2.4 Protocol Amendments

Below are listed the global protocol amendments and their impact on the statistical analysis plan.

Table 2.4-1: Changes to Protocol that Affect the Analyses

Document	Date of Issue	Summary of Change
Revised Protocol 03	24JUN2019	No changes with statistical implications.
Revised Protocol 02	16NOV2018	-Added a Data Monitoring Committee -Added text regarding treatment access rules: although open label, no summary analyses will be performed by treatment arm unless a planned interim analysis.
Revised Protocol 01	29JUN2018	-Modified PD-L1 stratification levels to 3 categories: (CPS ≥5%, CPS ≥ 1 to <5, or CPS < 1% (including indeterminate)) -Revised time period and frequency for collecting AE and SAE information extended to 135 days after last dose for all safety listings. -Updated CTCAE to version 5
Original Protocol	02APR2018	-Not applicable

2.5 Blinded Independent Review Committee

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 disease progression will be reviewed by the BICR. Details of BICR responsibilities and procedures will be specified in the BICR charter.

2.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized. A DMC will be established to provide oversight of safety and efficacy considerations. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for BMS-986213, or nivolumab, plus chemotherapy.

The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study.

3 OBJECTIVES

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
Primary Objective:	
To compare ORR of BMS-986213 in combination with chemotherapy, with ORR of nivolumab in combination with chemotherapy, by BICR, in randomized subjects with untreated, unresectable, and either locally advanced, or metastatic LAG-3 positive GC or GEJ adenocarcinoma.	ORR in subjects who are LAG-3 positive. ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects 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 Objectives:	
To assess the overall safety and tolerability of BMS-986213 in combination with chemotherapy vs. nivolumab in combination with chemotherapy in treated subjects 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 subjects 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 subjects with a BOR of CR or PR as assessed by the investigator using RECIST 1.1, divided by the number of randomized subjects 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 subjects with advanced or metastatic LAG-3 negative GC or GEJ	ORR in the LAG-3 negative group or overall is defined as above, as the number of subjects in each population with a BOR of CR or PR divided by the number of randomized

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
adenocarcinoma, and overall (across LAG-3 negative and positive groups).	subjects 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 chemotherapy in randomized subjects 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 subjects with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma, and in the overall population by BICR and by the investigator.	DOR in subjects with advanced or metastatic LAG-3 negative GC or GEJ adenocarcinoma and for subjects 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 subjects 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 subjects 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. Subjects 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

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
	tumor assessment on or prior to initiation of subsequent anticancer therapy. Subjects 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. Subjects receiving treatment beyond progression must continue tumor assessments until such treatment has been discontinued.
[redacted]	

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

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

4 ENDPOINTS

4.1 Efficacy Endpoints

Below are the detailed definitions of the efficacy endpoints.

4.1.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of randomized subjects who achieve a best response of confirmed complete response (CR) or confirmed partial response (PR) based on BICR assessments (using RECIST v1.1 criteria) divided by the number of all randomized subjects. If the objective is for a particular population (LAG3 positive, LAG3 negative), only that population is selected. Best Overall Response (BOR) is defined as the best response, as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 criteria or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. Confirmation of response is required at least 4 weeks after the initial response.

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

Time to Response

Time to Response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the BICR. TTR will be evaluated for responders (confirmed CR or PR) only.

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

4.1.2 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of the first documented tumor progression as determined by the BICR (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who neither progress nor die, DOR will be censored on the date of their last evaluable tumor assessment. DOR will be evaluated for responders (confirmed CR or PR) only. [redacted]

[redacted]

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

4.1.3 Progression-Free Survival

Two definitions are used for analysis of Progression-Free Survival (PFS). The primary definition accounts for subsequent therapy by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy. The secondary definition is irrespective of subsequent therapy and does not account for subsequent therapy.

Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST v1.1 criteria) is not considered progression for purposes of determining PFS.

[redacted]

The first on-study tumor assessment is scheduled to be conducted at 12 weeks (± 1 week) following randomization. Subsequent tumor assessments are scheduled every 6 weeks (± 1 week) up to 13 months, then every 12 weeks until disease progression.

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

4.1.3.1 Primary Definition of Progression-Free Survival (Accounting for Subsequent Therapy)

The primary definition of PFS (PFS truncated at subsequent therapy) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS:

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.
- Subjects who receive subsequent anti-cancer therapy prior to documented progression will be censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy.

- Subjects who did not have a documented progression and received subsequent anti-cancer therapy will be censored at the date of the last evaluable tumor assessment conducted on or prior to the initiation of the subsequent anti-cancer therapy.

Censoring rules for the primary definition of PFS (PFS truncated at subsequent therapy) are presented as follows and in Table 4.1.3.1-1.

Figure 4.1.3.1-1: PFS Primary Definition

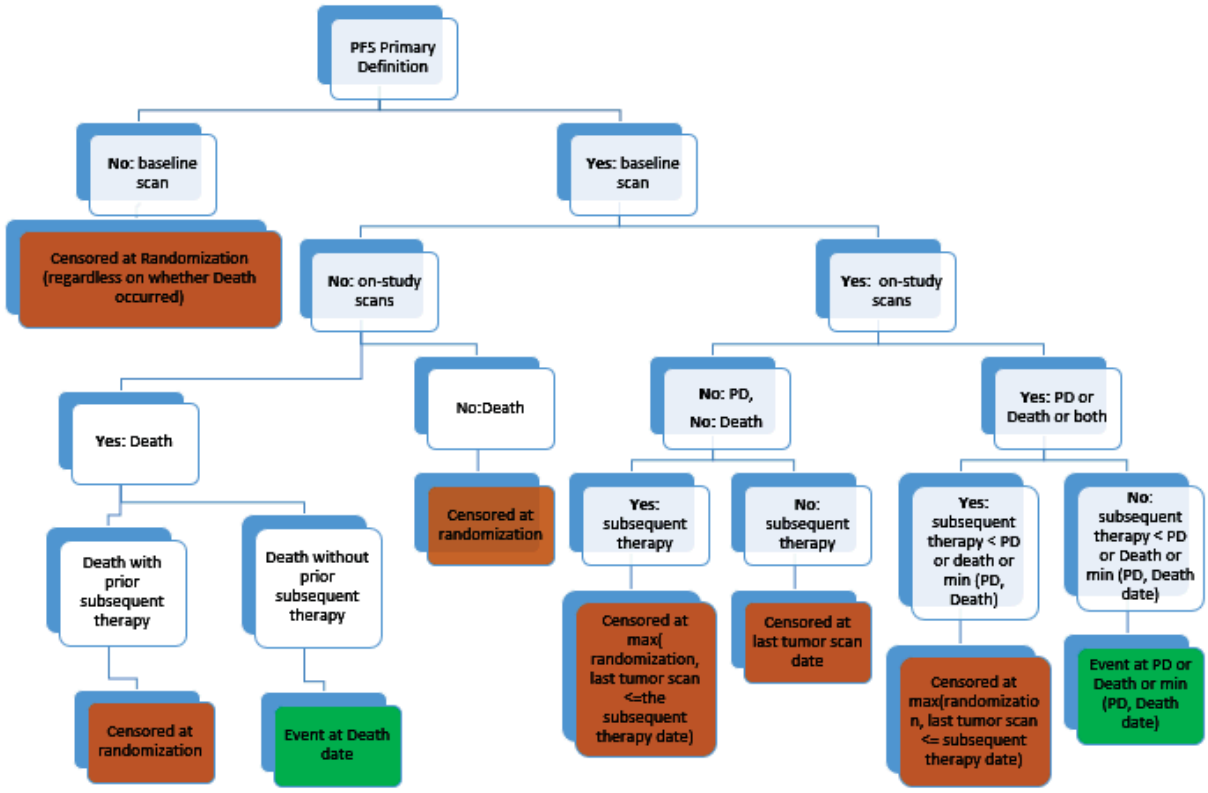


Table 4.1.3.1-1: Censoring Scheme used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of randomization	Censored
No on study tumor assessments and no death*	Date of randomization	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed

Table 4.1.3.1-1: Censoring Scheme used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

4.1.3.2 Secondary Definition of Progression Free Survival (Irrespective of Subsequent Therapy)

The secondary definition of PFS (ITT definition) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the secondary definition of PFS:

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

Censoring rules for the secondary definition of PFS (ITT definition) are presented as follows and in Table 4.1.3.2-1.

Figure 4.1.3.2-1: PFS Secondary Definition

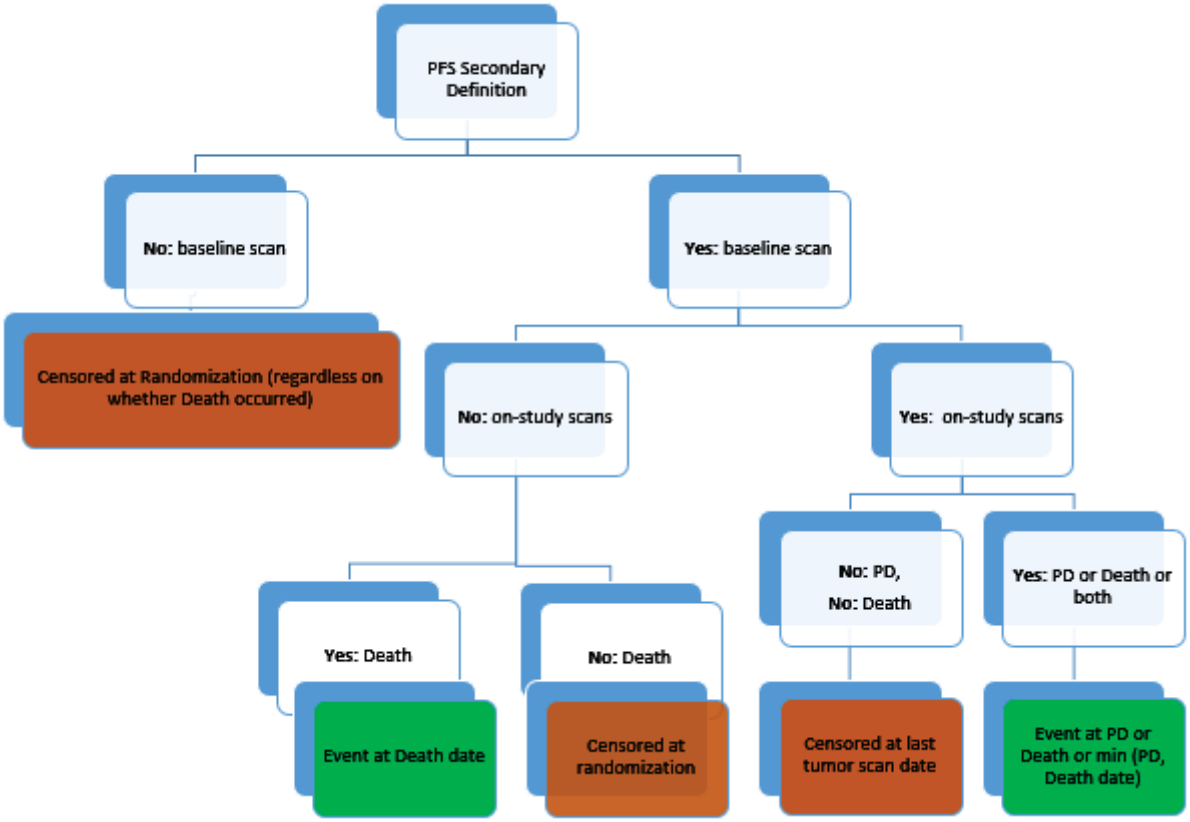


Table 4.1.3.2-1: Censoring Scheme for Secondary definition of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression per RECIST v1.1	Date of first documented progression per RECIST v1.1 criteria (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1	Date of death	Progressed

When the objective is specific to the investigator assessment, the above definition is altered to exchange BICR for investigator assessment in the derivation of the endpoint.

4.1.4 Overall Survival

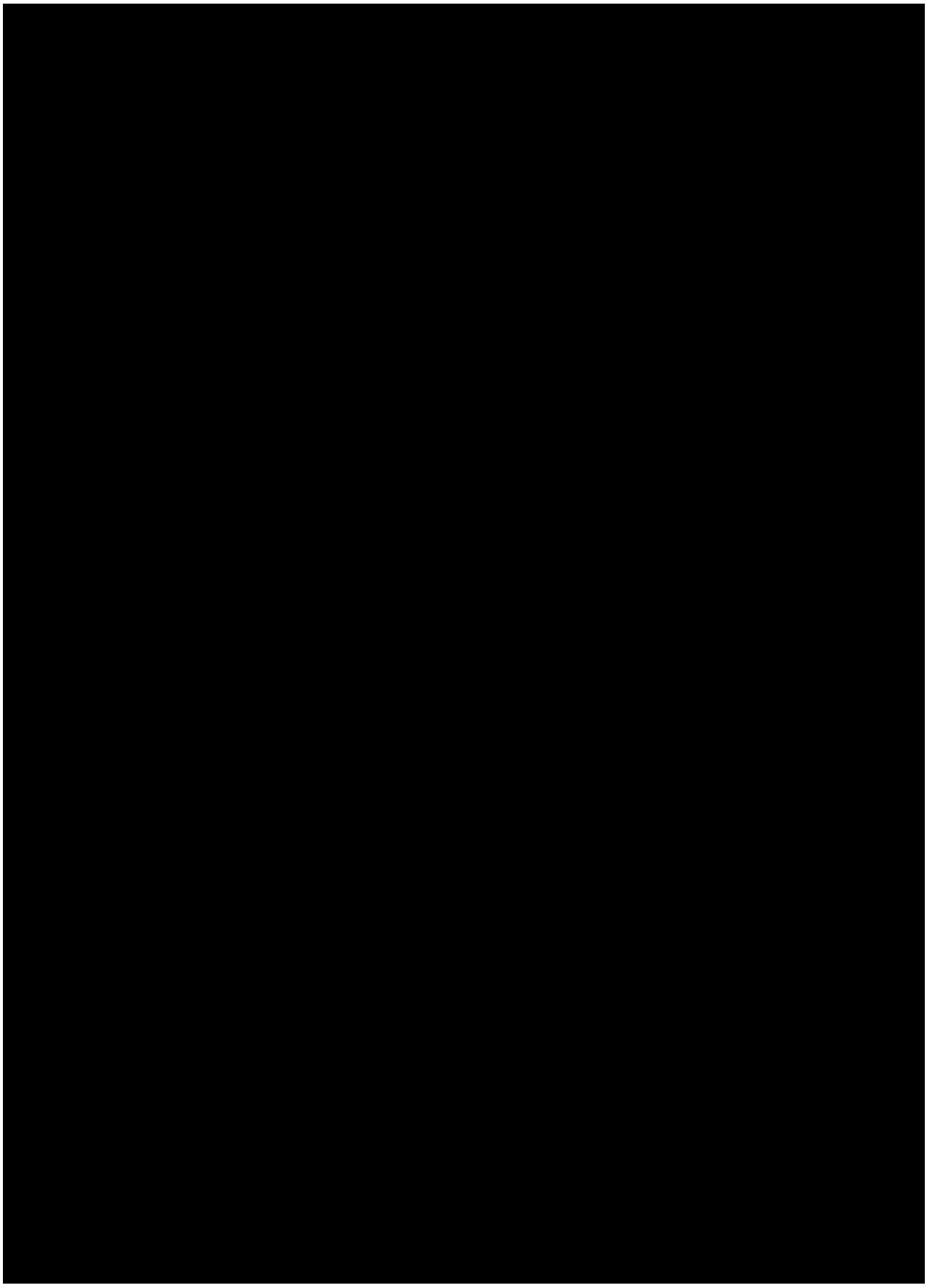
Overall survival (OS) is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact date (or "last known alive date"). Overall survival will be censored at the date of randomization for subjects who were randomized but had no follow-up.

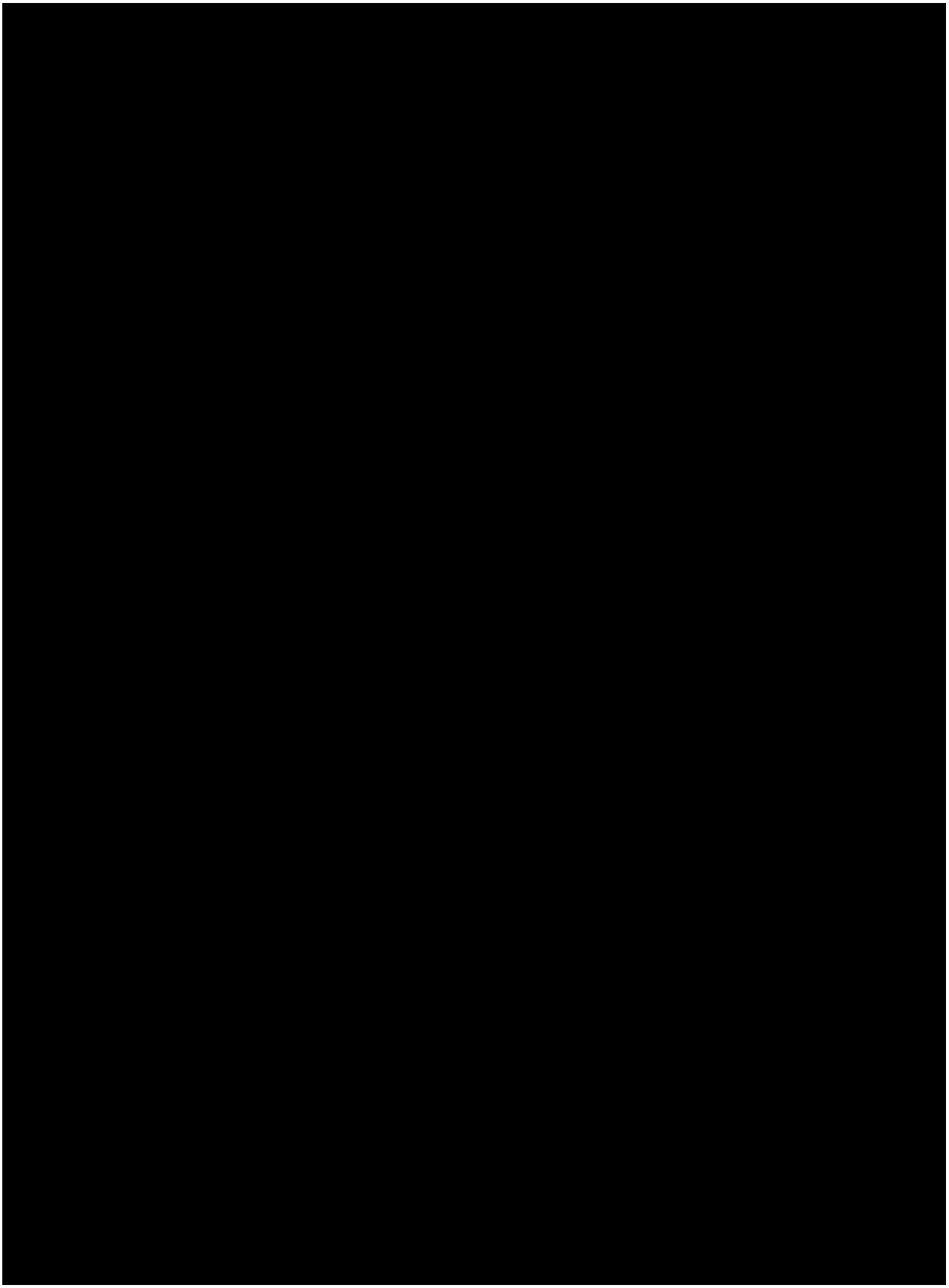
Survival follow-up will be conducted every 3 months after subject's off-treatment date.

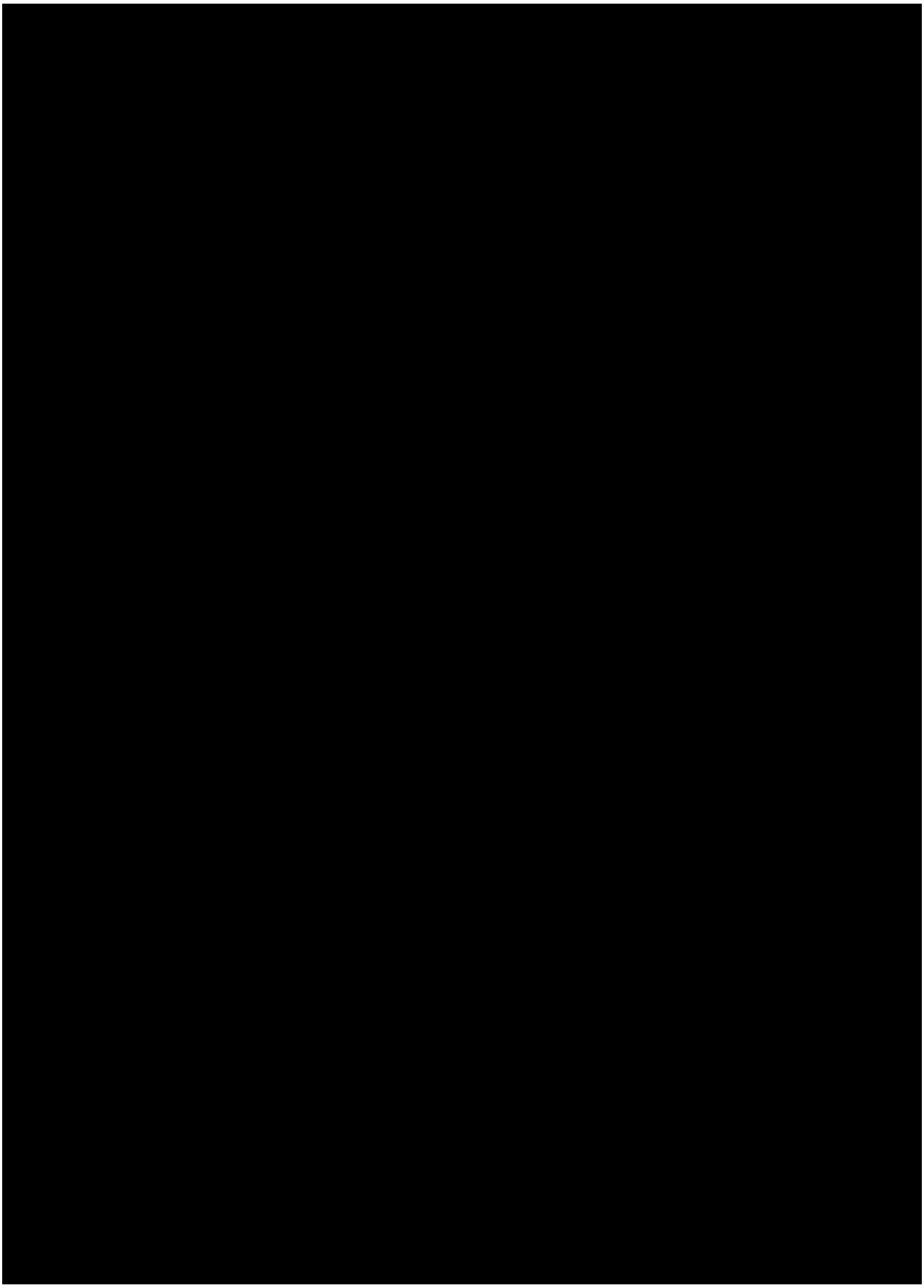
4.2 Safety Endpoints

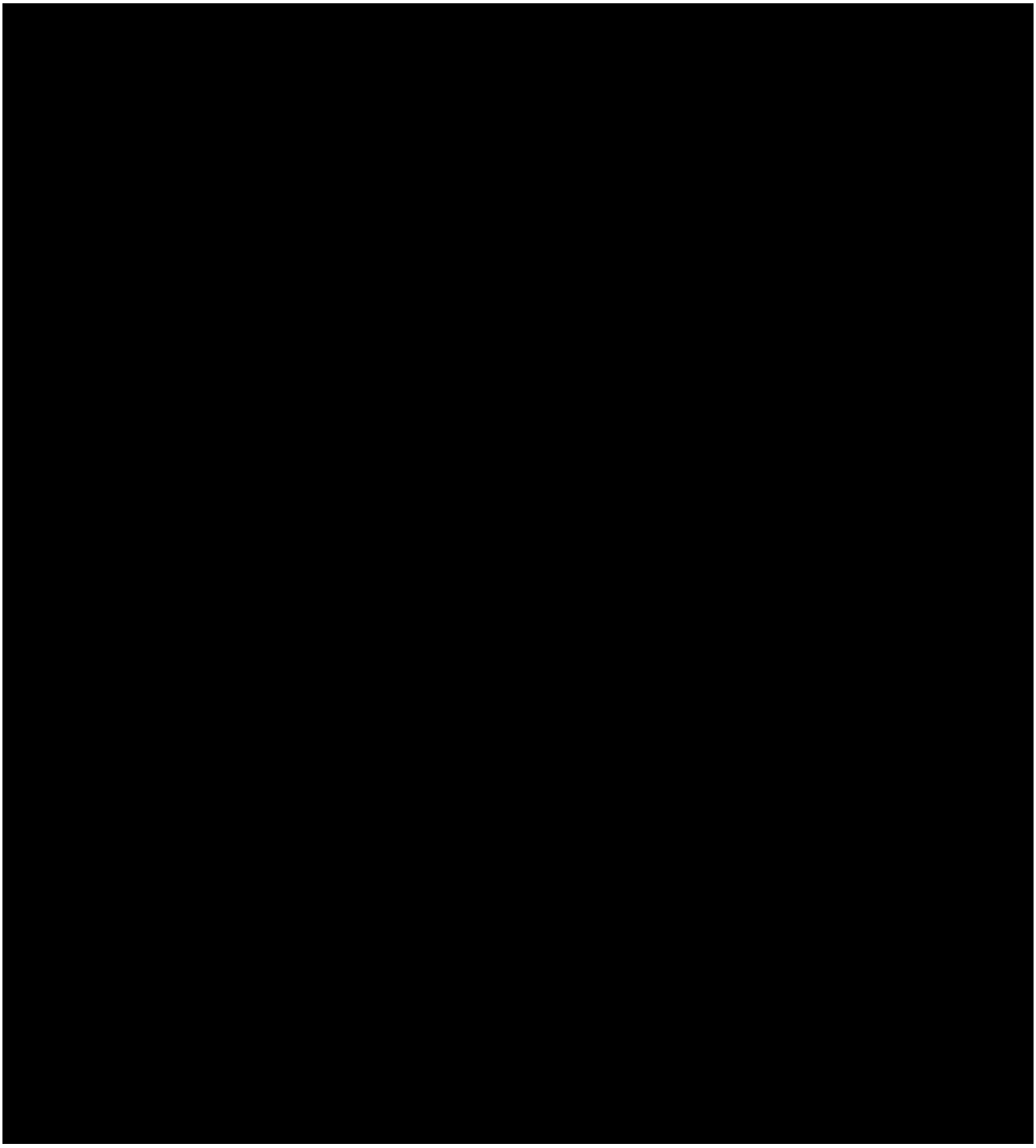
The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, adverse events leading to dose modification, select adverse events (select AEs) for EU/ROW Submissions, immune-mediated AEs (IMAEs) for US Submission, other events of special interest (OEOSI), and deaths. The use of immune modulating concomitant medication will be also summarized. In addition clinical laboratory tests [redacted] will be analyzed.

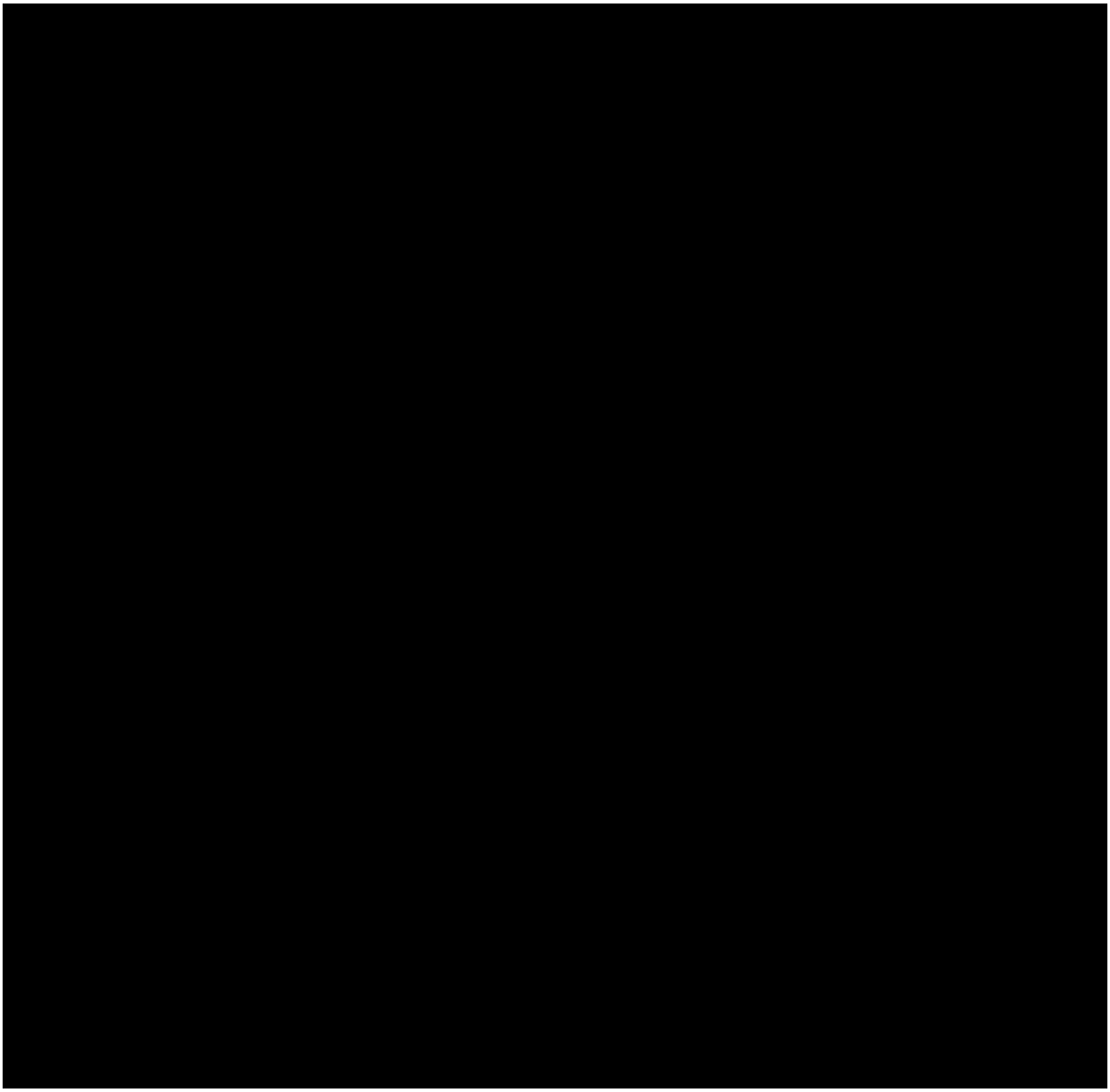
[redacted]











5 SAMPLE SIZE AND POWER

The sample size of the study is based on the primary objective, i.e., on the comparison of the ORR of subjects 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 subjects are expected to be randomized in a 1:1 ratio to the BMS-986213+chemotherapy or nivolumab+chemotherapy arms. 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]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Baseline period:
  - Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations (laboratory tests and vital signs) on the same date and time of the first dose of study treatment will be considered as baseline evaluations. Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:
    - Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment;
    - Baseline evaluations (laboratory tests and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment.
  - If there are multiple valid assessments on or prior to the first dose of study treatment:

- For laboratory tests, the latest non missing lab value on or before first dose date (and time if collected) will be used as the baseline in the analyses. For 'LIPASE' and 'GLUCOSE', for treated subjects only, the last predose assessment with non-missing toxicity grade will be considered as baseline. If multiple assessments exist with the same collection date (and time if collected) and entry date and time, then the first observation is used as baseline.
- For Eastern Cooperative Oncology Group (ECOG) performance status (PS), the latest ECOG PS value prior to or on the first dose date (and time if collected) will be used as the baseline in the analyses. If multiple records fall on the last date then the record with the highest value of ECOG PS will be considered as baseline.
- For LAG-3, among the records prior to or on first dose date, the latest record will be used as the baseline in the analyses. If there is more than one record for the latest date, then choose the one with the greatest specimen ID.
- For PD-L1, among the records prior to or on first dose date (and time if collected), identify first those with quantifiable test result. If there are no records with quantifiable test result, then select those with indeterminate result ("INDETERMINATE"). If there are no records with indeterminate test result, then select those with unavailable result ("NOT EVALUABLE). If there are no records with unavailable test result, then select those with not reported or not available result (all other records). The latest record will be used as the baseline in the analyses. If there is more than one record for the latest date, then choose the one with the greatest specimen ID.

[redacted]

- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
  - On-treatment evaluations (laboratory tests and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.
- Late-emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects who are off study treatment.

- In addition, data collected within an extended follow-up window of 135 days based on specific EU country requests, will be presented in listings.

6.2 Treatment Regimens

The treatment group "as randomized" corresponds to the treatment group assigned by the Interactive Response Technology (IRT) system.

Arm 1 in the IRT system: BMS-986213 Plus Chemotherapy

Arm 2 in the IRT system: Nivolumab Plus Chemotherapy

The treatment group "as treated" will be same as the treatment group "as randomized" by IRT unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject's treatment group "as treated" will be defined as the incorrect study treatment.

Unless otherwise specified, the safety analysis will be based on the treatment group "as treated".

Unless otherwise specified, the efficacy analysis will be based on the treatment group "as randomized".

6.2.1 Stratification

The randomization will be stratified by the following factors:

- LAG-3 expression (≥1% or <1%; no indeterminate allowed)
- PD-L1 expression status (CPS ≥ 5, CPS ≥ 1 to < 5, CPS < 1 or indeterminate).

[redacted]

Note: region (Japan/Taiwan [J/T] vs Rest of world [ROW]) was originally a stratification factor for the study, but no one from Japan/Taiwan enrolled in the study. Therefore, although it is still in the system as a stratification factor for the study, it will not be analyzed nor used as such.

6.3 Populations for Analyses

- Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.
- Randomized subjects: All subjects who were randomized through the IRT.
- Treated subjects: All randomized subjects who received at least one dose of any study treatment.

Unless otherwise specified, the safety analyses will include all treated subjects.

Unless otherwise specified, the efficacy analyses will include all randomized subjects.

All analyses will be performed using the treatment arm as randomized (intent to treat), with the exception of dosing and safety, for which the treatment arm as received will be used. For purposes of analysis, the following populations are defined in Table 6.3-1.

Specific to this study, subjects may receive three types of chemotherapy regimen (as per investigator's choice): XELOX, FOLFOX, or SOX. Chemotherapy regimen "as randomized" (referred to as "planned chemotherapy regimen") will be retrieved from the IRT system. Chemotherapy regimen "as treated" will be, in general, the same as the planned chemotherapy regimen. However, if a subject received the other chemotherapy regimen for the entire period of treatment, the subject's chemotherapy regimen will be defined as the regimen the subject actually received.

Table 6.3-1: Populations for Analyses

Population	Description
All Enrolled Subjects	All subjects who sign informed consent and were registered into the IRT.
All Randomized Subjects	All subjects who were randomized to either treatment arm. This population will be used for analyses of demography, protocol deviations, baseline characteristics, efficacy, and clinical outcomes assessments (must have baseline and on-study assessment).
All Treated Subjects	All subjects who received at least one dose of any study medication. This is the primary population for exposure and safety analyses.
All Treated LAG-3 Positive Subjects	All treated subjects in the LAG-3 positive (>= 1%) group. This is used for select disposition, exposure, and safety analyses.
All Treated LAG-3 Negative Subjects	All treated subjects in the LAG-3 negative (<1%) group. This is used for select disposition, exposure, and safety analyses.
All Randomized LAG-3 Positive Subjects	All randomized subjects in the LAG-3 positive (>= 1%) group. This is the dataset for primary efficacy analyses.
All Randomized LAG-3 Negative Subjects	All randomized subjects in the LAG-3 negative (<1%) group. This is the dataset for select efficacy analyses.
All Randomized Response Evaluable Subjects	All randomized subjects who had measurable lesions at baseline and one on study scan
[redacted]	

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarized by treatment group using the mean, standard deviation, median, minimum, and maximum values.

Time-to-event variables (e.g., time-to resolution) will be analyzed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method[8] (using log-log transformation for constructing the confidence intervals[9]).

The conventions to be used for imputing missing and partial dates for analyses requiring dates are described in Section 8.

7.1.1 Adverse Events, Serious Adverse Events, Multiple Events, Select Adverse Events, Other Events of Special Interest and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug was discontinued".

Adverse events leading to dose delay are AEs with action taken regarding study drug(s) = "Drug was delayed".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = "Dose was reduced".

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse event results will be graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) and the version of the criteria specified in the protocol will be used.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting will be done based on the 'Any Grade' column of the experimental arm when arms are presented side-by-side.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.9). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[10] in order to collapse adverse event records into unique records based on the preferred term. These data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- (Date of last dose of study treatment - date of first dose of study treatment + 31 days (or 101 days, depending on the analysis))/365.25, for subject who are off study treatment and were followed for at least 30 days (or 100 days, depending on the analysis) after last dose of study treatment.
- (Last known alive date - date of first dose of study treatment +1)/365.25, for subjects who are still on-treatment or who are off study treatment and were followed less than 30 days (or 100 days depending on the analysis) after last dose of study treatment.

7.1.1.1 Select Adverse Events (EU/ROW Submissions)

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g., pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. Categories of select AEs may include subcategories (e.g., adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

The list of MedDRA preferred terms used to identify select adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/subcategories.

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory of drug-related select AEs when applicable.

Further details on the definitions time-to onset and time-to resolution are described in APPENDIX 1.

7.1.1.2 Other Events of Special Interest

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category [redacted] The list of MedDRA preferred terms used to identify OEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.1.3 Immune-Mediated Adverse Events (US Submission)

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

[redacted]

7.2 Study Conduct

Enrollment by country and site, and enrollment by month will be summarized and listed for all enrolled subjects.

A by-subject listing of batch numbers for all treated subjects will be provided.

7.2.1 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized and listed based on the all randomized subjects, by treatment group and overall. In addition, this analysis will be performed using the All Randomized LAG-3 Positive Subjects. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through [redacted] listings.

At entrance deviations:

- Subject with baseline ECOG > 1
- Subject who received prior systemic anti-cancer therapy (adjuvant and neoadjuvant are allowed)
- Subject without histologically or cytologically confirmed diagnosis
- Subjects without measureable disease at baseline
- Subjects without PDL1 results (indeterminates are not deviations) prior to randomization
- Subjects without LAG3 results (indeterminates are deviations) prior to randomization
- Subjects with HER2 positive status (ihc3+ or fish positive ((her2:cep17 ratio >2) or (ihc2+/fish+))

On-treatment deviations

- Subjects who received anti-cancer therapy
- Subjects treated differently as randomized

7.3 Study Population

Analyses in this section will be tabulated for all randomized subjects by treatment group as randomized, unless otherwise specified.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed on the all enrolled subjects population only.

Number of subjects randomized but not treated along with the reason for not being treated will be tabulated by treatment group as randomized. This analysis will be performed on the All Randomized LAG-3 Positive Subjects, All Randomized LAG-3 Negative Subjects, and All Randomized Subjects.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject

status CRF page. This analysis will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

A by-subject listing for all treated subjects will be provided showing the subject's off treatment date and whether the subject continue in the study along with the reason for going off treatment period. A by-subject listing for all enrolled subjects will also be provided, showing whether the subject was randomized along with the reason for not being randomized.

Accrual will also be summarized by stratification factor, as stratified at IRT.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following baseline characteristics will be summarized by treatment arm as randomized. All baseline presentations identify subjects with missing measurements. This analysis will be performed on the All Randomized LAG-3 Positive Subjects, All Randomized LAG-3 Negative Subjects, and All Randomized Subjects.

Listings will also be provided.

- Age (continuous)
- Age category (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85; ≥ 75, ≥ 65)
- Sex (male, female)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)
- Race (White, Black or African American, Asian, Other)
- Region (Europe, North America, Rest of World, Asia)
- Country
- Time from Initial Disease Diagnosis to Randomization (1 year, >=1 year) (< 6months, 6months -< 1 year, 1-< 2 year, 2 - < 3 year, 3 -< 4 year, 4 - < 5 year, ≥ 5 year)
- ECOG performance status (0, 1)
- LAG-3 expression (LAG-3 expression (≥1%, <1%); no indeterminate allowed)
- PD-L1 expression (per IRT) (PD-L1 CPS ≥ 5, PD-L1 CPS ≥ 1 to < 5, PD-L1 CPS < 1 or indeterminate,)
- PD-L1 expression (per IRT) (PD-L1 CPS ≥ 1, PD-L1 CPS < 1 or indeterminate,)
- PD-L1 expression (per IRT) (PD-L1 CPS ≥ 5, PD-L1 CPS < 5 or indeterminate)
- Primary tumor location at initial diagnosis (GC, GEJ cancer)
- Disease stage at initial diagnosis (Stage I, Stage II, Stage III, Stage IV)
- Disease status (locally recurrent, metastatic, locally advanced)
- Lauren classification (intestinal type, diffuse type, mixed, unknown)
- Siewert-Stein classification (Type I, Type II, Type III)
- WHO histologic classification (adenosquamous carcinoma, mucinous adenocarcinoma, papillary serous adenocarcinoma, signet ring cell, tubular adenocarcinoma, other)
- TNM classification:

  - Tumor (Tx, T0, Tis, T1, T2, T3, T4, unknown)
  - Nodes (Nx, N0, N1, N2, N3, unknown)
  - Metastasis (Mx, M0, M1, unknown)
- Smoking status (current/former, never smoker, unknown)
- CNS metastases (yes/no)
- Liver metastases (yes/no)
- Peritoneal metastases (yes/no)
- HER-2 status at study entry (negative, positive, unknown)
- [redacted]
- EBV status (positive, negative, unknown)
- H.pylori (no, yes, unknown)
- Baseline hemoglobin (<10 g/dL; ≥ 10 g/dL)
- Baseline albumin (< LLN, ≥ LLN)
- Number of organs with baseline lesion (target or non-target; ≤ 1, >= 2) outside primary location (gastric, gastroesophageal junction and esophagus)
- All lesions at Baseline (Investigator and BICR): sites of disease, number of disease sites per subject, number of subjects with no measurable lesion
- Target Lesions (Investigator and BICR): Presence of target lesions, site of target lesion, sum of diameters of target lesions

Summary tables (cross-tabulations) by treatment group for stratification factor will be provided to show any discrepancies between what was reported through IRT vs. other data sources at baseline. This summary will be performed on the relevant populations based on all randomized subjects.

- PD-L1 expression level (CPS ≥ 5, CPS ≥ 1 to < 5, CPS < 1 or indeterminate) (IRT vs. clinical database)
- LAG-3 expression (<1%; ≥1%)

A listing of randomization scheme presenting randomized treatment group and as treated treatment group will be provided for all randomized subjects.

7.3.3 Medical History

A by-subject listing of general medical history for all randomized subjects will be provided.

7.3.4 Prior Therapy Agents

Prior therapy will be summarized for the relevant populations based on all randomized subjects.

Prior anti-cancer therapy:

- Setting of prior systemic therapy regimen received (adjuvant, metastatic disease, neo-adjuvant)
- Time from completion of prior adjuvant/neo-adjuvant therapy to treatment (for subjects who received prior adjuvant/neo-adjuvant therapy), (< 6 months, 6 -< 12month, ≥ 12 months)

- Prior surgery related to current cancer (yes or no)
- Prior radiotherapy (yes or no)
- Prior systemic therapy classified by therapeutic class and generic name

Other Prior therapy:

- Prior/current non-study medication classified by anatomic and therapeutic classes

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Physical Examinations

Subjects with abnormal baseline physical examination will be listed by subject.

7.3.6 Baseline Physical Measurements

Baseline physical measurements will be listed by subject.

7.4 Extent of Exposure

Listings will include all available exposure data. Analyses will be performed on the relevant populations by treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group. These analyses will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Number of doses/cycles received (summary statistics)
- Cumulative dose
- Duration of treatment
  - using a KM curve whereby the last dose date will be the event date for those subjects who are off study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.

A by-subject listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Key parameters used to characterize dosing data are found in Table 7.4.1-1, 7.4.1-2, and 7.4.1-3.

Table 7.4.1-1: Administration of Study Therapy for Subjects Treated with XELOX

	BMS-986213 or Nivolumab	Oxaliplatin	Capecitabine
Dosing schedule per protocol	Rela 120mg + Nivo 360mg (BMS-986213) Q3WK, IV or Nivo 360mg Q3WK, IV	130mg/m2 Q3WK, IV	1000mg/m2 Q3WK, oral
Dose*	Dose is defined as Total Dose administered (mg). Dose administered in mg at each dosing date are collected on the CRF	Total dose administered (mg) / most recent BSA	Total dose administered (mg) / most recent BSA
Cumulative Dose	The sum of all doses (mg) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period
Relative Dose Intensity (%)	Cumulative dose (mg) / [Last rela dose date – rela Start dose date + 21) x 120/21] Cumulative dose (mg) / [Last nivolumab dose date – nivolumab Start dose date + 21) x 360/21]	Cumulative dose (mg/m2) / [Last oxaliplatin dose date – oxaliplatin Start dose date + 21) x 130/21]	Cumulative dose (mg/m2) / [First dose of capecitabine in the last cycle – capecitabine Start dose date + 21) x 2000/21]
Duration of Treatment	Last dose date (of the last administered study therapy) - Start dose date (of the first administered study therapy) + 1		

* Dose administered in mg at each dosing date and BSA (computed using recent weight and baseline height) are collected on the CRF.

Table 7.4.1-2: Administration of Study Therapy for Subjects Treated with FOLFOX

	BMS-986213 or Nivolumab	Oxaliplatin	Leucovorin	Fluorouracil
Dosing schedule per protocol	Rela 160mg + Nivo 480mg (BMS-986213) Q4WK, IV or Nivo 480mg Q4WK, IV	85mg/m2 Q2WK	400mg/m2 Q2WK	**Bolus 5-FU:** 400mg/m2 Q2WK, IV on Day 1 of the cycle **Continuous 5-FU:** 1200mg/m2 Q2WK, IV continuous infusion on Day1-2 of the cycle
Dose*	Dose is defined as Total Dose administered (mg). Dose administered in mg at each dosing date are collected on the CRF	Total dose administered (mg) / most recent BSA	Total dose administered (mg) / most recent BSA	Total dose administered (mg) / most recent BSA
Cumulative Dose	The sum of all doses (mg) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period
Relative Dose Intensity (%)	Cumulative dose (mg) / [Last rela dose date – rela Start dose date + 28) x 160/28] Cumulative dose (mg) / [Last nivolumab dose date – nivolumab Start dose date + 28) x 480/28]	Cumulative dose (mg/m2) / [Last oxaliplatin dose date – oxaliplatin Start dose date + 14) x 85/14]	Cumulative dose (mg/m2) / [Last leucovorin dose date – leucovorin Start dose date + 14) x 400/14]	**Bolus 5-FU:** Cumulative dose (mg/m2) / [First dose of fluorouracil in the last cycle – fluorouracil Start dose date + 14) x 400/14] **Continuous 5-FU:** Cumulative dose (mg/m2) / [First dose of continuous fluorouracil in the last cycle – continuous fluorouracil Start dose date + 14) x 1200/14]
Duration of Treatment	Last dose date (of the last administered study therapy) - Start dose date (of the first administered study therapy) + 1			

* Dose administered in mg at each dosing date and BSA (computed using recent weight and baseline height) are collected on the CRF.

Table 7.4.1-3: Administration of Study Therapy for Subjects Treated with SOX

	BMS-986213 or Nivolumab	Oxaliplatin	S-1 (tegafur/gimeracil/oteracil)
Dosing schedule per protocol	Rela 120mg + Nivo 360mg (BMS-986213) Q3WK, IV or Nivo 360mg Q3WK, IV	130mg/m2 Q3WK, IV	S-1 (tegafur/gimeracil/oteracil) BID, oral (administered as 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, 60 mg/dose)
Dose*	Dose is defined as Total Dose administered (mg). Dose administered in mg at each dosing date are collected on the CRF	Total dose administered (mg) / most recent BSA	Total dose administered (mg) / most recent BSA
Cumulative Dose	The sum of all doses (mg) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period	The sum of all doses (mg/m2) administered to a subject during the treatment period
Relative Dose Intensity (%)	Cumulative dose (mg) / [Last rela dose date – rela Start dose date + 21) x 120/21] Cumulative dose (mg) / [Last nivolumab dose date – nivolumab Start dose date + 21) x 360/21]	Cumulative dose (mg/m2) / [Last oxaliplatin dose date – oxaliplatin Start dose date + 21) x 130/21]	BSA <1.25m2: Cumulative dose (mg/m2) / [First dose of S-1 in the last cycle – S-1 Start dose date + 14) x 1,120/14] BSA ≥1.25 and < 1.5 m2: Cumulative dose (mg/m2) / [First dose of S-1 in the last cycle – S-1 Start dose date + 14) x 1,400/14] BSA ≥1.5 m2: Cumulative dose (mg/m2) / [First dose of S-1 in the last cycle – S-1 Start dose date + 14) x 1,680/14]
Duration of Treatment	Last dose date (of the last administered study therapy) - Start dose date (of the first administered study therapy) + 1		

* Dose administered in mg at each dosing date and BSA (computed using recent weight and baseline height) are collected on the CRF.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Table 7.4.2.1-1: Dose Delays

	Q4W BMS-986213 or Nivolumab	Q3W BMS-986213 or Nivolumab	XELOX	FOLFOX	SOX
Specifications per Protocol					
Dose considered as actually delayed	If the delay is exceeding 3 days	If the delay is exceeding 3 days	Per package insert or local standard	Per package insert or local standard	Per package insert or local standard
Maximum delay allowed between doses	42 days	42 days	Not specified	Not specified	Not specified
Definitions for the Analysis					
Dose Delay	duration of preceding cycle in days – 28	duration of preceding cycle in days – 21	duration of preceding cycle in days – 21	duration of preceding cycle in days – 14	duration of preceding cycle in days – 14
Categories of dose delays	on-time, 4 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days	on-time, 4 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days	on-time, 4 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days	on-time, 3 – 4, 5 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days	on-time, 4 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days

The following parameters will be summarized by treatment arm:

- Number of dose delayed per subject, Length of Delay and Reason for Dose Delay

Reason for dose delay will be retrieved from CRF dosing pages.

7.4.2.2 Dose Interruptions

Each study therapy may be interrupted. This information will be retrieved from CRF dosing pages. (For capecitabine and S-1, which are oral, interruption will be programmatically derived.)

The following parameters will be summarized by treatment arm:

- Number of subject with at least one dose infusion interrupted along with reason for the interruptions and number of infusions interrupted per subject

7.4.2.3 IV Rate Reductions

For each study therapy dosed as IV (BMS-986213, nivolumab, oxaliplatin, leucovorin, and fluorouracil) IV rate may be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment arm:

- Number of subject with at least one IV rate reduction along with reason for the IV rate reduction and number of infusions with IV rate reduced per subject

7.4.2.4 Dose Escalations

Dose escalations of BMS-986213 or nivolumab are not permitted.

7.4.2.5 Dose Reductions

Dose reductions of BMS-986213 or nivolumab are not permitted.

7.4.2.6 Dose Omissions

Dose reductions of BMS-986213 or nivolumab are not permitted.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the UMC WHO Drug Global Dictionary.

The following summary table will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

The following summary table will be provided:

- Prior/current medications (subjects with any prior/current medication, subjects by medication class and generic term)

A by-subject listing(s) will accompany the table(s).

7.4.3.1 Immune Modulating Medication

Immune modulating concomitant medications are medications entered on an immune modulating medication form or available from the most current pre-defined list of immune modulating medications. The list of anatomic class, therapeutic class and generic name used for the selection at the time of the database lock will be provided.

The percentage of subjects who received immune modulating concomitant medication for

- management of adverse event
- premedication
- other use
- any use
- management of drug-related select adverse event (any grade, grade 3-5) by select AE category/ subcategory (EU/ROW Submissions)
- management of IMAEs (any grade, grade 3-5) by IMAE category (US Submission) will be reported separately for each treatment group (percentages of treated subjects by medication class and generic term).

For each category/subcategory of drug-related select AEs (any grade, grade 3-5) and IMAEs (any grade, grade 3-5), the following will be reported for each treatment group:

- The total immune modulating medication treatment duration (excluding overlaps), duration of high dose of corticosteroid, initial dose of corticosteroid, and tapering duration (summary statistics)

Duration represents the total duration the subject received the concomitant medication of interest. If the subject took the medication periodically, then DURATION in the summation of all use. Initial dose represents the dose of the concomitant medication of interest received at the start of the event. In the case multiple medications started on the same date, the highest equivalent dose is chosen and converted to mg/kg by dividing by the subject's recent weight.

These analyses, except the ones related to IMAEs will be conducted using the 30-day safety window. The analyses related to IMAEs will be conducted using the 100-day safety window.

7.4.3.2 Subsequent Cancer Therapy

- Number and percentage of subjects receiving subsequent therapies will be summarized. Categories include:
  - Immunotherapy including commercial Nivolumab (anti-PD1 agents, anti-PD-L1 agents, anti-CTLA-4 agents and others) by drug name
  - Other anti-cancer agents excluding all immunotherapy (approved and investigational) by drug name
  - Surgery for treatment of tumors
  - Radiotherapy for treatment of tumors
  - Any combination of the above
- A subject listing of follow-up therapy will also be produced for subjects who had any subsequent therapy

7.5 Efficacy

Principal analyses of objective response rate (ORR) and progression free survival (PFS) will be based on the Blinded Independent Central Review (BICR) evaluation, unless noted otherwise.

Unless stated otherwise, whenever a stratified analysis is specified in the all randomized population, the following stratifications factors (recorded at randomization as per IRT) will be used, except for the analysis in LAG-3 positive or LAG-3 negative sub-groups when only PDL1 CPS expression will be used.

- LAG-3 expression (≥ 1% or < 1%; no indeterminate allowed)
- PD-L1 expression status (CPS ≥ 5, CPS ≥ 1 to < 5, CPS < 1 or indeterminate)

There will be no p-values presented for any of the analyses other than the primary endpoint. All other analyses will be descriptive in nature. Confidence intervals for all endpoints will be at the two-sided 95% level. Point estimates and confidence bounds for efficacy variables will be rounded to the second decimal place.

7.5.1 Analysis of Objective Response Rate (ORR)

Primary (and secondary) objectives of the study are to compare ORR per BICR between treatment groups among LAG-3 positive (primary objective) and among LAG-3 negative (secondary objective) randomized subjects.

The number and percentage of subjects in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented, by treatment group, for each LAG-3 population and overall. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson[11] will be presented, by treatment group for each LAG-3 population and overall.

ORR as assessed by BICR will be compared between treatment groups using a two-sided Cochran-Mantel-Haenszel test stratified by PD-L1 status ((CPS ≥5%, CPS ≥ 1 to <5, or CPS < 1% (including indeterminate)) as recorded in the IRT. These analyses and associated 70% CIs for ORR difference will be performed on the All Randomized LAG-3 Positive Subjects (primary population), All Randomized LAG-3 Negative Subjects, and All Randomized Subjects.

The following subject-level graphics will also be provided:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response, progression, last dose received, and death
- For response evaluable subjects (defined per RECIST 1.1 as randomized subjects with baseline and at least one on-study tumor assessment)
  - A bar plot showing the best % reduction from baseline in sum of diameter of target lesions based on BICR assessment for each subject will be produced (excluding assessments after PD and assessments after start of subsequent anti-cancer therapy)
  - A plot of individual time course of tumor burden change per BICR assessment will be produced

Similar analyses will be repeated based on the investigator's assessment of ORR. A cross tabulation of BICR best response versus the investigator best response will be presented, by treatment group and by response categories. Concordance Rate of Responders will be computed as the frequency with which investigator and BICR agree on the classification of a subject as responder vs. non responder/UTD as a proportion of the total number of randomized subjects (using relevant populations) assessed by both the investigator and BICR.

[redacted]

[redacted]

7.5.3 Time to Response and Duration of Response

Duration of response (DOR) and time to response (TTR) will also be evaluated for subjects who achieved confirmed PR or CR. The DOR for each treatment group. The DOR will be estimated using the Kaplan-Meier (KM) product limit method and will be displayed graphically. A table will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians. Median values of DOR, along with two-sided 95% CI in each treatment group will be computed based on a log-log transformation method. These analyses will be performed on the All Randomized LAG-3 Positive Subjects, All Randomized LAG-3 Negative Subjects, and All Randomized Subjects.

The status of subjects who are censored in the DOR KM analysis will be tabulated for each randomized treatment group including the following categories:

- Ongoing follow-up (current [last scan within adequate window vs cutoff date], not current)
- Off-study (lost to follow-up, withdraw consent, never treated)
- Received subsequent anticancer therapy

TTR, which does not involve censoring, will be summarized by treatment group in all responders using descriptive statistics.

- A by-subject listing will be presented including treatment group, time to response, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

Similar analyses will be repeated based on the investigator's assessment of ORR.

7.5.4 Analysis of Progression-Free-Survival

One of the objectives of the study is to assess the difference in progression-free survival (as determined by BICR) between treatment groups in the LAG-3 positive, LAG-3 negative, and all randomized populations.

The analysis of PFS (as determined by BICR) will be to compare the two treatment groups via stratified log-rank test among all randomized subjects at a two-sided $\alpha = 0.30$ level.

The primary definition of PFS adjusting for subsequent anticancer therapy will be used in this analysis.

The estimate of the PFS hazard ratio between treatment groups will be calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties will be handled using the exact method. A two-sided 70% CI for the hazard ratio will also be presented.

The PFS function for each treatment group will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS in each treatment group will be computed via the log-log transformation method. [redacted] These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will

be derived based on Greenwood[14] formula for variance derivation and on log-log transformation applied on the survivor function[15].

The source of PFS event (progression or death) will be summarized by treatment group.

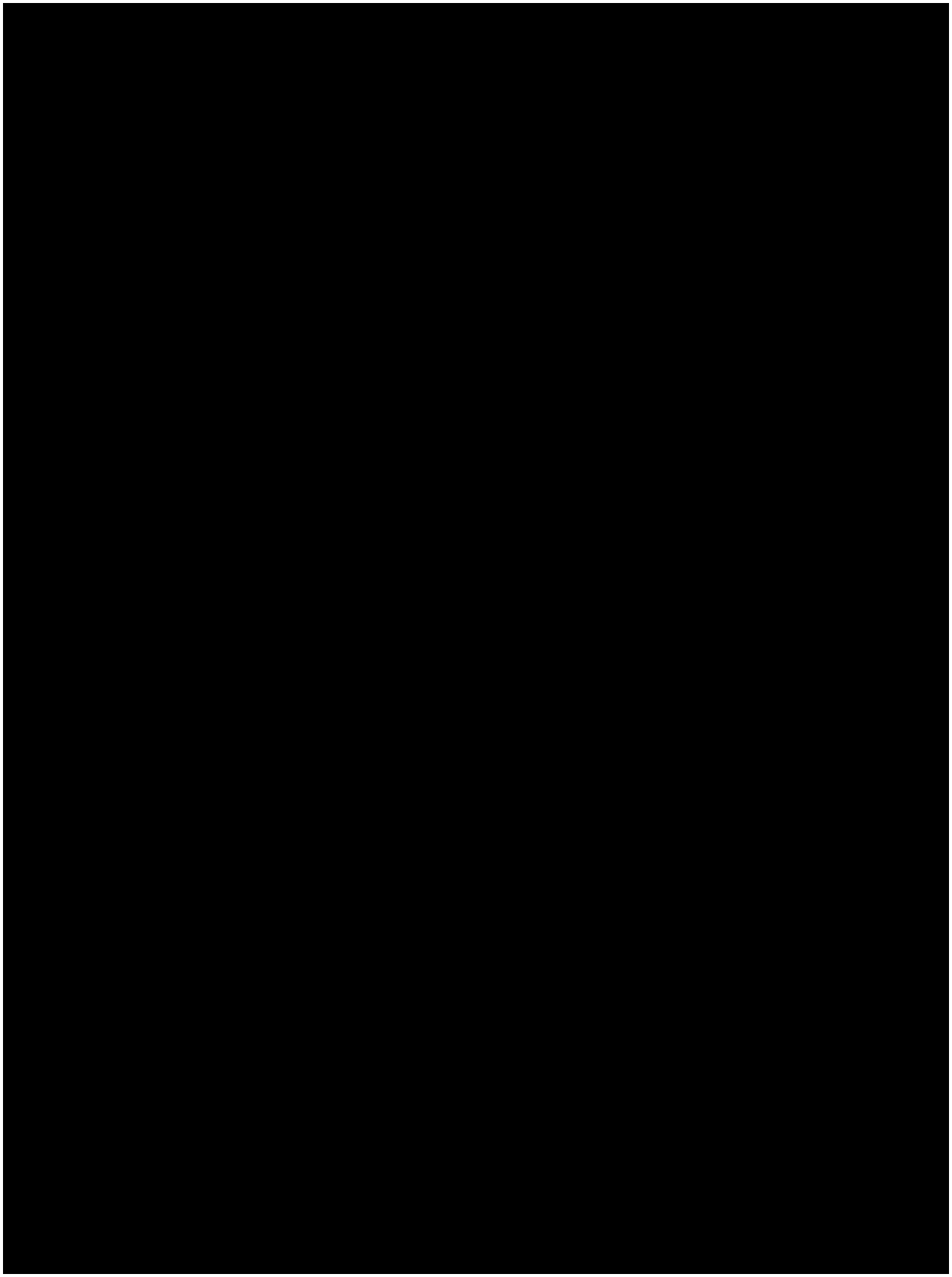
Analyses of PFS may also be conducted based on the secondary definition of PFS. These analyses will be the same as those specified above.

The status of subjects who are censored (as per primary definition of PFS) in the PFS KM analysis will be tabulated for each randomized treatment group including the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)
- No baseline tumor assessment
- No on-study tumor assessment and no death
- Received subsequent anticancer therapy

Similar analyses will be repeated based on the investigator's assessment of progression.

[redacted]



[redacted]

7.5.7 Analysis of Overall Survival

One of the objectives of the study is to assess the difference in overall survival between treatment groups in each of the randomized populations.

Overall survival will be compared between the treatment groups, using stratified log-rank test. The stratification factors will be those used in the analysis of PFS. The stratified hazard ratio between the treatment groups will be presented along with 70% CI.

OS will be estimated using the KM techniques. A two-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method. OS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)

[redacted]

7.5.8 Current Status of PFS and OS Follow-up

The extent of follow-up for survival, defined as the time between randomization date and last known alive date (for subjects who are alive) or death date (for subjects who died), will be summarized descriptively (median, min, max) in months for all randomized populations.

The currentness of follow-up for survival, defined as the time between last OS contact (i.e., last known alive date or death date) and cutoff date (defined by last patient last visit date), will be summarized in months for all randomized subjects. Subjects who died and subjects with last known alive date on or after data cut-off date will have zero value for currentness of follow-up.

Minimum follow-up for OS, defined as the time from cutoff date to last subject's randomization date, will be summarized in months for all randomized subjects.

Time from last evaluable tumor assessment to cutoff date in months will be summarized by treatment group and overall for all randomized subjects. Subjects who have a PFS event will be considered as current for this analysis. The secondary definition of PFS will be used for this summary.

By-subject listing will also be produced to accompany the subject time from last evaluable tumor assessment.

7.5.9 Interim analysis of Overall Survival

Interim analysis for OS will be performed at the time of the primary database lock.

7.6 Safety

Analyses in this section will be tabulated for all treated subjects by treatment group as treated, unless otherwise specified.

7.6.1 Deaths

Deaths will be summarized by treatment group. These analyses will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

- All deaths, reasons for death
- Deaths within 30 days of last dose received, reasons for death
- Deaths within 100 days of last dose received, reasons for death

A by-subject listing of deaths will be provided for the all enrolled subjects population.

7.6.2 Serious Adverse Events

Serious adverse events will be summarized by treatment group. These analyses will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

All analyses will be conducted using the 30-day safety window.

A by-subject SAE listing will be provided for the "enrolled subjects" population.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by treatment group. These analyses will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

The analyses will be conducted using the 30-day safety window.

A by-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized by treatment group:

- Overall summary of AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of related AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

The analysis will be conducted using the 30-day safety window.

A by-subject AEs leading to dose delay/reduction listing will be provided.

7.6.5 Adverse Events

Adverse events will be summarized by treatment group.

The following analyses will be conducted using the 30 days safety window only:

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT. This analysis will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects, and All Treated Subjects by Chemotherapy
- Overall summary of any AEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall summary of any non-serious AEs presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group
- Overall summary of any AEs that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT. This analysis will be performed on the All Treated LAG-3 Positive Subjects, All Treated LAG-3 Negative Subjects, and All Treated Subjects.

The following analyses will be conducted using the 30 days safety window and repeated using the 100 days safety window:

- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT

A by-subject AE listing will be provided. A by-subject listing of any AE requiring immune modulating medications will also be provided.

7.6.6 Select Adverse Events (EU/ROW Submissions)

Unless otherwise specified, analyses will be performed by select AE category. Analyses will also be repeated by subcategory of endocrine events.

7.6.6.1 Incidence of Select AE

Select AEs will be summarized by treatment group for each category/subcategory.

The following analyses will be conducted using the 30-day safety window only:

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT
- Overall summaries of any serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT
- Overall summaries of drug-related serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT
- Overall summaries of any select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT
- Overall summaries of drug-related select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT
- Summary of frequency of unique select AEs by Category

A by-subject select AE listing will be provided.

7.6.6.2 Time-to Onset of Select AE

Time-to onset of drug-related select AEs (any grade, grade 3-5) will be summarized for each category/subcategory by treatment group.

Time-to onset analyses are restricted to treated subjects who experienced at least one drug-related select AE in the category/subcategory. The analyses will be conducted using the 30-day safety window.

Additional details regarding the time-to onset definition are described in time-to onset definition subsection of APPENDIX 1.

7.6.6.3 Time-to Resolution of Select AE

Time-to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of drug-related select AE (any grade, grade 3-5) by treatment group
- Time-to resolution of drug-related select AE (any grade, grade 3-5) where immune modulating medication was initiated, by treatment group

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. Time-to resolution where immune modulating medication was initiated analyses are restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest select AE.

The analyses will be conducted using the 30-day safety window.

The following summary statistics will be reported: percentage of subjects with resolution of the longest select AE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

See time-to resolution definition subsection of APPENDIX 1 for additional details.

7.6.7 Immune-Mediated Adverse Events (US Submission)

IMAEs will be summarized by treatment group for each immune-mediated category / PT using the 100-day safety window:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT
- Overall summary of endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Overall summary of non-endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT
- Overall summary of endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Overall summary of non-endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT
- Overall summary of endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Summaries of time-to onset and time-to resolution of non-endocrine IMAEs where immune modulating medication was initiated presented by Category
- Summaries of time-to onset and time-to resolution of endocrine IMAEs presented by Category

A by-subject listing of IMAEs will be provided. By-subject listings of time-to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided. For new studies which collect investigator assessment of potential IMAE data, a by-subject listing of AEs considered as immune-mediated events per investigator but not qualified for IMAEs definition will also be provided.

7.6.8 Other Events of Special Interest

OEOSI will be summarized by treatment group for each category.

The following analyses will be conducted using the 100-day safety window:

- Overall summary of OEOSI by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT
- Overall summary of drug-related OEOSI by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

A by-subject listing of OEOSI will be provided.

7.6.9 Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs

- A table showing the total number and rate (exposure adjusted) of occurrences for AEs occurring in at least 5% of subjects in any treatment group

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided. No formal comparisons will be made between treatment groups.

7.6.10 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

7.6.10.1 Hematology

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.10.2 Serum Chemistry

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: ALT, AST, alkaline phosphatase (ALP), total bilirubin and creatinine.

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.10.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low), and Glucose Serum (fasting hyperglycemia and hypoglycemia regardless of fasting status).

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.10.4 Additional Analyses

In addition, further analyses on specific laboratory parameters will be performed by treatment group:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- ALP > 1.5 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test.

- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these specific abnormalities will be provided.

7.6.11 Vital Signs

Vital signs collected on the CRF will be provided in a listing. CG and echocardiogram results will also be listed and summarized by treatment group

7.6.12 Physical Measurements

Physical measurements will be listed by subject.

[redacted]

7.6.14 Pregnancy

A by-subject listing of pregnancy tests results will be provided for randomized female subjects.

7.6.15 Adverse Events By Subgroup

Overall summary of any AEs and drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT and for each treatment group for the following subgroups:

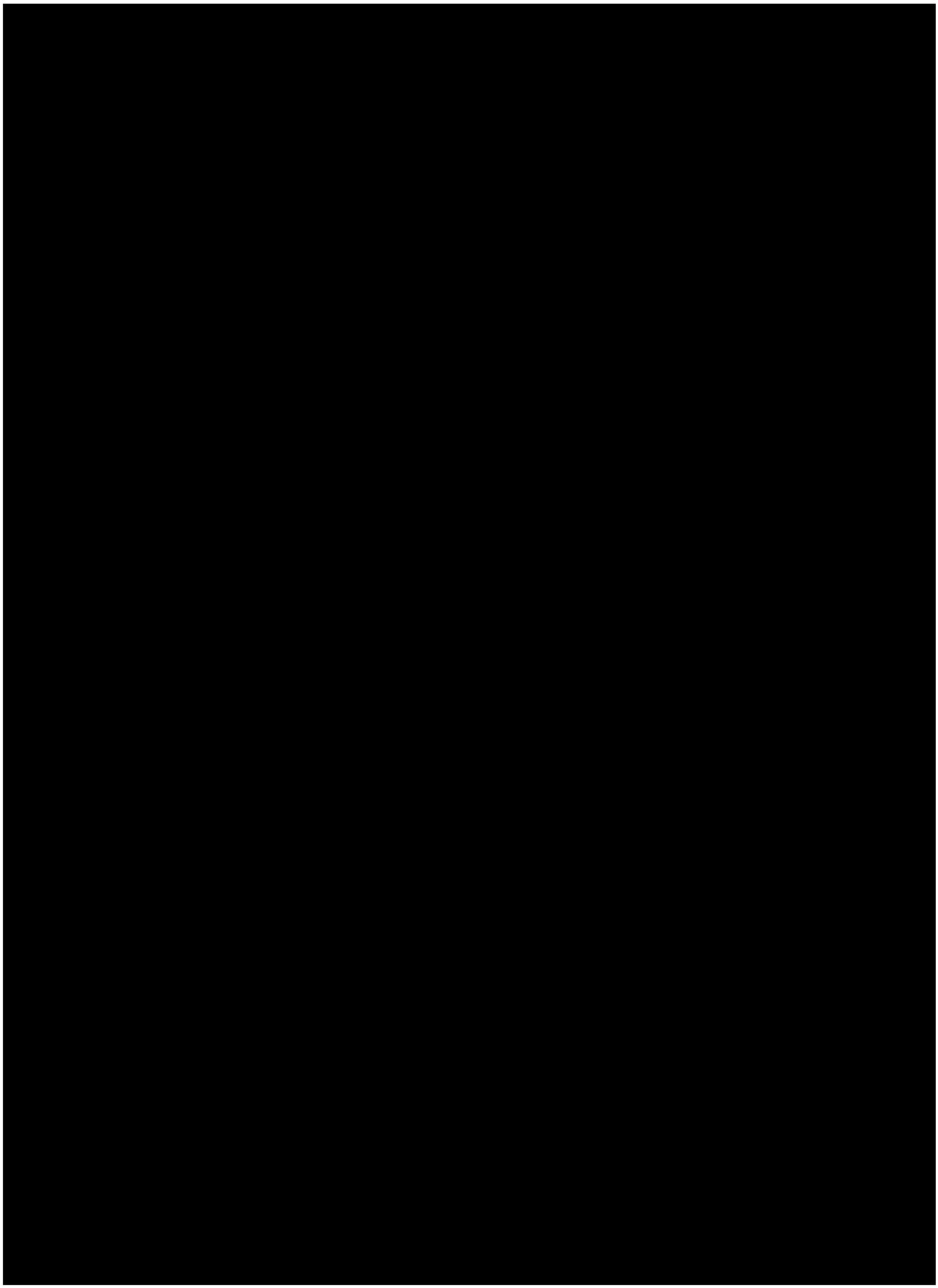
- Sex (Male vs. Female)
- Race
- Age (< 65 vs. 65 - < 75 vs. 75 - < 85 vs. ≥ 85 vs. ≥ 75 vs. ≥ 65)

These analyses will be conducted using the 30-day safety window only.

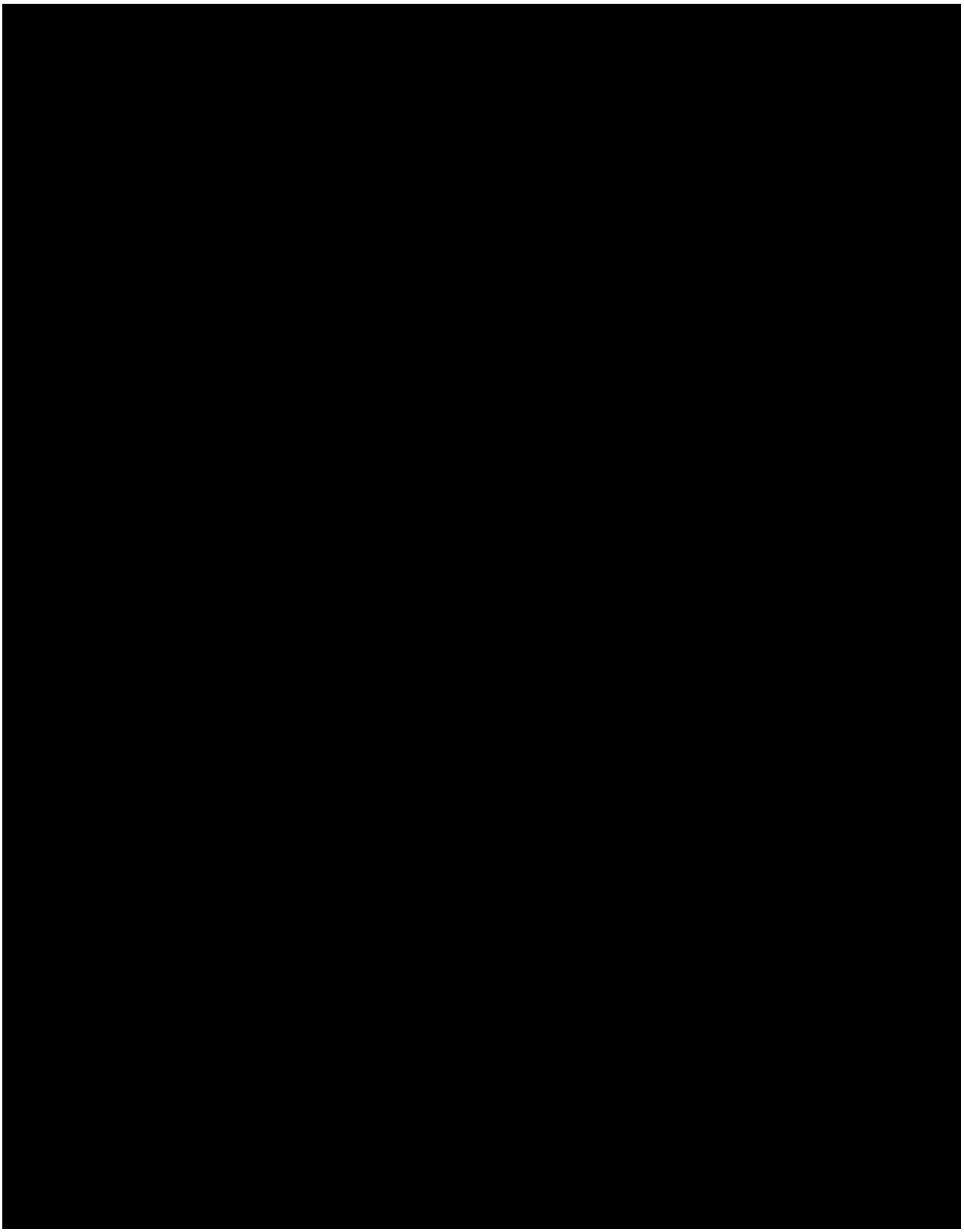
[redacted]

[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

8 CONTENT OF REPORTS

All analyses describe in this SAP will be included in the Clinical Study Report except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

9 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[16]
- For missing and partial adverse event resolution dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[17].
- Missing and partial radiotherapy and surgery dates will be imputed using algorithm described in APPENDIX 2.
- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known alive date.
  - If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.
- For date of progression after start of study therapy, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

- For date of progression to prior therapies, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For other partial/missing dates, the following conventions were used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, "July 1" will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Date	Author	Description
1	06APR2020	[redacted]	Original version
2	14JUL2020		-changed PD-L1 CPS stratification factor to consistently have 3 categories throughout document [redacted] -Sections 2.1, [redacted] and 6.2.1- added information on CPS rescore for certain subjects and the rescore will be the primary value used for those subjects. [redacted] -updated wording of PD-L1 in multiple spots to read PD-L1 CPS. Section 8 was switched with section 9 so conventions come at the end of the SAP. -Section 7.2.1 - added analysis for All Randomized LAG-3 Positive Subjects -Section 7.3.2 - added RACE display and REGION display. [redacted] -Section 2.1 - changed the wording for the FU and survival visits to take directly from the protocol. [redacted]

APPENDIX 1 TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to onset of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed "clustered" AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table 10-2 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs experienced by the subject in this category per adverse event criteria category. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the subject started an immune modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 10-2: Derivation of Clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

APPENDIX 2 MISSING AND PARTIAL RADIOTHERAPY AND SURGERY DATES IMPUTATION ALGORITHMS

Procedures – Imputation Rules.

If reported procedure start date is a full valid date then set start date equal to the date part of procedure start date.

In case of partial date use imputation rules described below:

- If only day is missing then
  - If month and year of procedure match month and year of first dose date then impute as date of first dose;
  - If month and year of procedure don't match month and year of first dose date then impute as first day of that month and year.
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

Note: Imputation is not applicable to data where start date is not collected (for example "PRIOR RADIOTHERAPY" CRF). Set start date to missing in this case.

If reported end date is a full valid date then set end date equal to the date part of the reported end date.

In case of partial date use imputation rules described below:

- If reported end date is partial then set end date equal to the last possible reported end date based on the partial entered reported end date.
- If reported end date is missing, continuing, unknown or invalid then set end date equal to the most recent database extraction date.

If end date was imputed then compare end date to the death date or last known alive date if subject is not dead. If posterior then end date should be imputed to death date (or last known alive date if subject not dead).

Note: Imputation of partial dates only applies to data entered on "RADIOTHERAPY" CRF page. For other CRF pages in case of partial dates set end date to missing.

Surgeries – Imputation Rules.

If reported surgery date is a full valid date then set start date equal to the date part of surgery date.

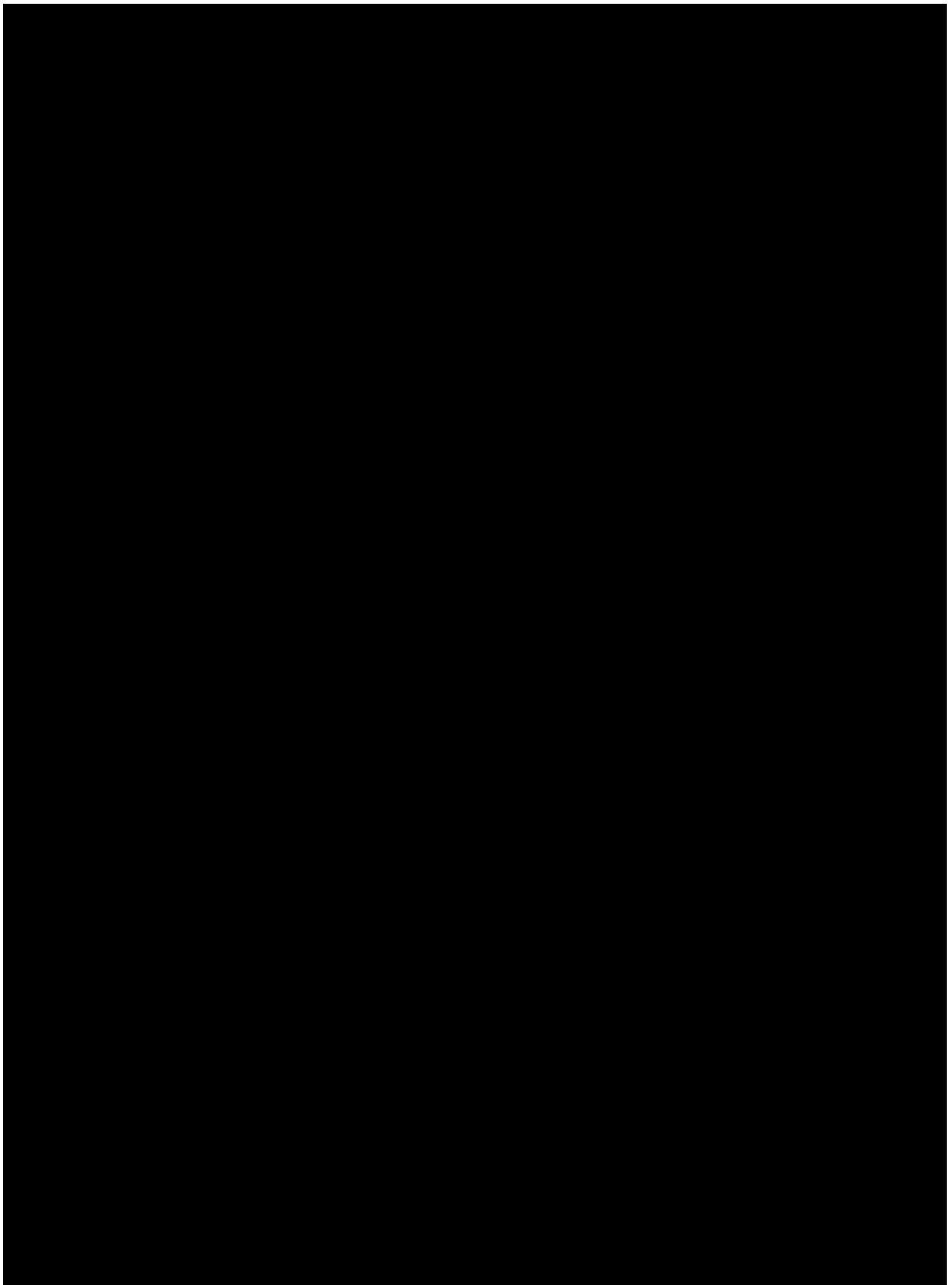
In case of partial date, use one of the two imputation rules described below:

A. For data collected on "PRIOR SURGERY RELATED TO CANCER" CRF page:

- If only day is missing then impute as the first day of the month;
- If both day and month are missing then then impute as 01JAN of the year;
- If date is completely missing or invalid then leave missing.

B. For data collected on other CRF pages (deemed to be on-treatment/subsequent surgeries):

- If only day is missing then
  - If month and year of surgery match month and year of first dose date then impute the missing date as the date of first dose;
  - If month and year of surgery don't match month and year of first dose date then impute as first day of that month and year;
- If both day and month are missing then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.



[redacted]

11 REFERENCES

[8] Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982

[9] Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag

[10] Global Biometric Sciences, SAS Analysis Dataset Specification, Unique Adverse Events. Version 2.0, April 22, 2015

[11] Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika* **26**: 404–413.

[14] Greenwood, M. The errors of sampling of the survivorship tables, Reports on Public Health and Statistical Subjects, 33, Appendix 1, HMSO, London, 1926

[15] Kalbfleisch, J. D. and Prentice, R. L. (1980), The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.

[16] Adverse Event Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.3.0 April 23, 2018

[17] Non-Study Medication Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.10.0 April 23, 2018