Official Title of Study:

A Phase 2 Randomized Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy as First Line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

NCT Number: NCT04623775

Document Date (Date in which document was last revised): 11 Sep 2024

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CLINICAL PROTOCOL CA224104

A Phase 2 Randomized Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy as First Line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

Short Title:

A Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy in Participants with Stage IV or Recurrent NSCLC

Protocol Amendment Number: 07

Incorporates Administrative Letters 03, 04 and 05

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	11-Sep-2024	Major changes include: • End of Study definition extended to include final date on which data is to be collected for survival follow-up. The last visit definition is added for clarity. • Options have been added for treatment continuation for actively treated patients showing clinical benefit, after end of study. • The number of blood collections for biomarkers, PK, and questionnaires have been reduced to reduce patient and site staff burden. [redacted] • Information in Administrative Letters 03, 04 and 05 have been incorporated. Administrative letter 02 information has been superseded in this amendment; hence, content is not incorporated in this Amendment. • Additional updates added to align the administrative references with EU CTR.
Protocol Amendment 06	19-May-2022	[redacted] • Added in recommendation for antibiotics to treat sub-clinical infection prior to randomization in the presence of elevated neutrophil and white blood counts at baseline, and the resolution of active infections prior to first dose of study treatment. Part 2 updated to an open-label design. • Updated chemotherapy options in Part 2. • Primary and secondary endpoints in Part 2 updated to ORR and PFS, respectively. [redacted] • Other minor revisions include clarifications to scheduling of safety laboratory, biomarker and pharmacokinetic collections, eligibility criteria, and duration of contraception for male and female participants after last dose of chemotherapy.
Protocol Amendment 05	[redacted]	[redacted]

Document	Date of Issue	Summary of Change
		[redacted]
Protocol Amendment 04	01-Dec-2021	• Stratification factors for randomization in Part 2 updated to include ECOG performance status in addition to histology and PD-L1 level. Gender and LAG-3 expression level removed as stratification factors. [redacted] • The time requirements for the use of contraception and for pregnancy monitoring have been updated to align with program wide specification for relatlimab. • Non-live COVID vaccinations have been evaluated as a concomitant medication with no expected interaction with study treatments as stated in the Benefit/Risk section.
Protocol Amendment 03	30-Jul-2021	[redacted]

Document	Date of Issue	Summary of Change
		[redacted]
Protocol Amendment 02	16-Apr-2021	Aligns the immunotherapy dose modification criteria and immune-related adverse event management algorithms with CTCAE v5, clarifies serologic testing and includes vaccine information for SARS-CoV-2, clarifies infusion duration [redacted], and adds instructions for location of specific management guidelines for severe adverse reactions.
Protocol Amendment 01	11-Nov-2020	Clarifies inclusion/exclusion criteria and aligns the concomitant medication section with the US product label of chemotherapy agents.
Original Protocol	18-Aug-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

Amendment 07 incorporates the following changes in the protocol to provide options to participants showing clinical benefit to continue to receive study drug after closure of the study. To accommodate these options, the end of study definition was revised.

- End of Study definition extended to include final date on which data is to be collected for survival follow-up. The last visit definition is added for clarity.
- Allow options for patients to continue to receive study treatment regimen after end of study.
- Decreased number of blood collections for PK, biomarkers, and questionnaires (PROs) to reduce patient and site staff burden.
- [redacted]
- Incorporation of information of Administrative Letters 03, 04 and 05.
- Additional updates made to align the administrative references with EU CTR.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	• Updated Medical Monitoring contact information. • Sponsor address information updated. • Eudra CT Number changed to EU CT Number.	• Incorporation of Administrative Letters 05. • Administrative change. • Administrative change.
Table 2-2: On Treatment Procedural Outline (CA224104), Table 2-3: Follow-up and Survival Procedural Outline (CA224104), Table 4-1: Objectives and Endpoints, [redacted]	[redacted]	The collection and testing of the samples are no longer required for this study. Reducing the number of sample collections for PK [redacted] will reduce patient and site staff burden.
	• Updated PRO collection ([redacted] PGIS, [redacted] and PGIC) to cap at Cycle 36 for part 1 and every	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	6 cycles from cycle 36 until end of study for part 2.	
Section 5.3: End of Study Definition	End of Study definition extended to include final date on which data is to be collected for survival follow-up. The last visit definition is added for clarity	Provide options to participants showing clinical benefit to continue to receive study drug after closure of the study
Table 7-1: Study Treatments for CA224104	Row 2: Nivolumab packaging information is updated to "4 or 5 vials per carton".	This information is updated as part of administrative letter 04.
Section 8.2.1: Treatment after discontinuation of the study	Added details for study drug treatment options for study participants, after end of study.	Allow participants who are demonstrating clinical benefit to continue the study drug regimen after the study closure
Section 9.1.2: Patient-reported outcomes	Updated PRO collection [redacted] PGIS, [redacted] and PGIC) to cap at Cycle 36 for part 1 and every 6 cycles from cycle 36 until end of study for part 2	Reducing the number of PRO assessments will reduce patient burden.
Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Relatlimab and Nivolumab and Pharmacokinetic Sampling Schedule for Chemotherapy Drugs	Sample collection timepoints are updated for Pharmacokinetics and Immunogenicity sampling.	Sufficient number of PK samples have been collected to conduct Population PK (PopPK) and Exposure-response analyses with efficacy and safety endpoints, as well as assessment of potential impact of immunogenicity on efficacy and safety endpoints. Therefore, PK and ADA sample collection beyond 2 years of treatment is no longer required and will be removed from this protocol to reduce patient burden.
Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Relatlimab and Nivolumab and Pharmacokinetic Sampling Schedule for Chemotherapy Drugs	Row 11 is updated to add "or maximum of two years of treatment"	This information is updated as part of administrative letter 03

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor edits, formatting, and typographical corrections.	Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 2 Randomized Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy as First Line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

Short Title:

A Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy in Participants with Stage IV or Recurrent NSCLC

Study Phase: Phase 2

Rationale:

Nivolumab, relatlimab, and platinum doublet chemotherapy (PDCT) each have non-overlapping anti-cancer mechanisms and may have synergistic and/or additive activity as combination therapy, with few overlapping toxicities. Lymphocyte-activation gene 3 (LAG-3) is often expressed on chronically exhausted T-cells and is frequently co-expressed with programmed death-ligand 1 (PD-L1) on tolerized tumor-infiltrating lymphocytes (TILs) across tumor types. The rationale for combining a LAG-3 inhibitor and an anti-programmed cell death protein 1 (PD-1)/PD-L1 agent originates from evidence suggesting that LAG-3 has a potential role in T-regulatory cells suppression and anti–PD-1 resistance. The current standard of care, anti-PD-(L)1 (± anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] antibody) in combination with PDCT has demonstrated significant improvement in overall survival (OS) as well as progression-free survival (PFS) in participants with previously untreated metastatic non-small cell lung cancer (NSCLC).

There are several candidate biomarkers which may select participants who will benefit from the addition of relatlimab to nivolumab plus chemotherapy. Multiple clinical trials have established the correlation between PD-L1 expression and increased response to PD-1 and PD-L1 immune checkpoint inhibition. Data from CA224020 demonstrated preliminary evidence that participants with LAG-3 expression are more likely to respond to treatment with relatlimab in combination with nivolumab. Recently, fibrinogen-like protein 1 (FGL-1) was identified as a new ligand for LAG-3 that is responsible for its T-cell inhibitory function and potentially a new mechanism for immuno-evasion. Therefore, FGL-1 may be a novel biomarker to predict outcomes of anti-PD-1 and anti-LAG-3 tumor therapies.

The benefit of the relatlimab plus nivolumab combination continues to be explored in several types of metastatic malignancies. The combination of nivolumab 360 mg every 3 weeks (Q3W) plus relatlimab 720 mg or 360 mg Q3W and 4 cycles of PDCT is expected to have a synergistic effect in the first line (1L) NSCLC population based on the clinical activity shown by the 2 individual combinations (nivolumab plus relatlimab and nivolumab plus PDCT) and their distinct but complementary mechanisms of action.

The hypotheses of study CA224104 are as follows:

- Part 1 (Dose safety confirmation): Nivolumab, 360 mg, plus relatlimab, 720 mg or 360 mg Q3W combined with 4 cycles of PDCT is safe in participants with 1L Stage IV or recurrent NSCLC.
- Part 2: Nivolumab plus relatlimab combined with 4 cycles of PDCT improves ORR when compared to nivolumab plus PDCT in participants with 1L Stage IV or recurrent NSCLC.

Study Population:

Adult participants with histologically confirmed Stage IV or recurrent NSCLC with no prior systemic therapy for metastatic disease, no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS-1, or B-rapidly accelerated fibrosarcoma proto-oncogene (BRAF)V600E mutations, and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1.

Key Inclusion Criteria:

- Males and females; ≥ 18 years of age or local age of majority.
- Histologically confirmed metastatic NSCLC of squamous (SQ) or non-squamous (NSQ) histology with Stage IV or recurrent disease following multi-modal therapy for locally advanced disease.
- Measurable disease by computed tomography or magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria; radiographic tumor assessment performed [redacted] before randomization.
- No prior systemic anti-cancer treatment given as primary therapy for advanced or metastatic disease.
- ECOG PS of ≤ 1 at screening and confirmed prior to randomization.
- Participants must have a life expectancy of at least 3 months at the time of first dose.

[redacted]

Key Exclusion Criteria:

- Women who are pregnant or breastfeeding.
- Participants with EGFR, ALK, or ROS-1 mutations which are sensitive to available targeted inhibitor therapy. All participants with NSQ histology must have been tested for EGFR, ALK,

or ROS-1 mutation status. Participants with NSQ histology and unknown EGFR, ALK, or ROS-1 status are excluded.

- Participants with known BRAFV600E mutations that are sensitive to available targeted inhibitor therapy. Participants with unknown or indeterminate BRAF mutation status are eligible.
- Participants with untreated central nervous system metastases.
- Participants with leptomeningeal metastases (carcinomatous meningitis).
- Concurrent malignancy requiring treatment.
- Participants with an active, known, or suspected autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

[redacted]

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Part 1: Dose Safety Confirmation	
Primary	
To evaluate the proportion of participants with TRAEs leading to discontinuation within 12 weeks after the first dose of nivolumab plus 2 different dose levels of relatlimab (360 mg and 720 mg) in combination with PDCT in dose safety evaluable participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• TRAEs leading to discontinuation within 12 weeks after the first dose
Secondary	
To evaluate the safety and tolerability of nivolumab plus 2 different doses of relatlimab (360 mg and 720 mg) in combination with PDCT in all participants with histologically confirmed 1L Stage IV or recurrent NSCLC that were treated during the dose safety confirmation period	• Incidence of TRAEs leading to discontinuation, AEs, SAEs, and select AEs
Part 2	
Primary	
To evaluate ORR of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• ORR per RECIST v1.1 by BICR
Secondary	
To evaluate the PFS of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• PFS per RECIST v1.1 by BICR

Table 1: Objectives and Endpoints

Objectives	Endpoints
To evaluate the duration of response (DoR) of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• DoR per RECIST v1.1 by BICR, including DoR at 6, 12 and 18 months
To evaluate ORR and PFS of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC, in subgroups defined by PD-L1 expression, LAG-3 expression, FG-L1 expression	• ORR and PFS per RECIST v1.1 by BICR
To evaluate the safety and tolerability of nivolumab plus relatlimab in combination with PDCT in histologically confirmed 1L Stage IV or recurrent NSCLC.	• Incidence of AEs, SAEs, TRAEs, IMAEs and select AEs

Abbreviations: 1L = first line; AE = adverse events; BICR = blinded independent central review; FG-L1 = fibrinogen-like protein 1; LAG-3 = lymphocyte-activation gene 3; NSCLC = non-small cell lung cancer; ORR = overall response rate; PDCT = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression free survival; RECIST = response evaluation criteria in solid tumors; SAE = serious adverse event; TRAE = treatment related adverse events.

Overall Design:

This multi-center, randomized trial will evaluate the efficacy and safety of the combination of nivolumab plus relatlimab and PDCT vs nivolumab and PDCT in adults with untreated Stage IV or recurrent NSCLC. The study will be carried out in 2 parts: Part 1, a site-and-subject blind dose safety confirmation and Part 2, a open-label, randomized, controlled trial.

Part 1 - Dose safety confirmation (n ≈ up to 120): Site-and-subject blinded, randomized dose safety confirmation. Eligible participants will be randomized 1:1 to Arms A or B to evaluate the safety and tolerability of the combination of nivolumab plus relatlimab 720 mg and PDCT and confirm the safety profile. The relatlimab 360 mg Q3W dose in Arm B will be evaluated to generate additional safety data at this dose level. The randomization will be stratified by histology (SQ vs NSQ). After all treated participants have been followed-up for a minimum of 12 weeks, the primary analysis will take place to determine whether the final established threshold for the dose-safety evaluable population has been met and to evaluate the totality of the Part 1 safety data. In addition, the proportion of treatment-related adverse events (TRAEs) leading to discontinuation within 12 weeks of the first dose will be monitored for each arm [redacted]

Part 2 (n = 300): Randomized, open-label, controlled trial that will further evaluate the efficacy and safety of the nivolumab, relatlimab plus chemotherapy combination vs nivolumab plus chemotherapy. [redacted] At this time, participants that are in screening and found to be eligible will be randomized 1:1 into experimental Arm C or control Arm D of Part 2 of the trial. [redacted]

[redacted] The stratification factors for randomization in Part 2 are histology (SQ vs NSQ), ECOG performance status (0 vs 1) and PD-L1 level (≥ 1% [including NQ] vs < 1%).

Number of Participants:

In the dose safety confirmation (Part 1), up to approximately 120 participants will be randomized 1:1 to treatment Arms A or B (ie, 60 participants per arm).

In Part 2, approximately 300 participants will be randomized 1:1 to the experimental arm, C, or the control arm, D (ie, 150 participants per arm).

Sample Size Determination: Part 1

Up to approximately 120 participants will be randomized 1:1 to treatment Arms A and B (ie, up to 60 participants per arm). [redacted]

Sample Size Determination: Part 2

Approximately 300 participants will be randomized 1:1 (ie, 150 participants per arm) stratified by histology (SQ vs NSQ). ECOG PS (0 vs 1) and PD-L1 level (≥ 1% [including NQ] vs < 1%). [redacted]

Treatment Arms and Duration:

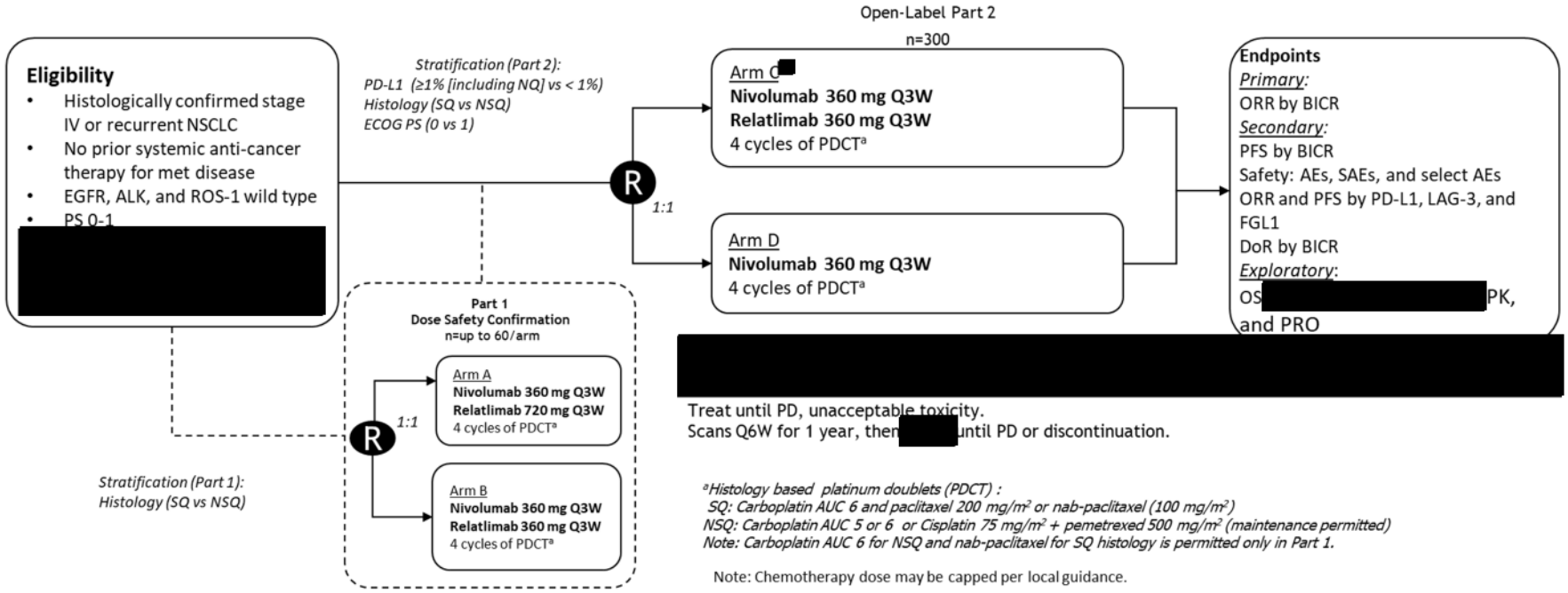
Study treatment:

Study Treatment for CA224104		
Medication	**Potency**	**IP/Non-IP**
Relatlimab	[redacted]	IP
Nivolumab	10 mg/mL	IP
Carboplatin	10 mg/mL	IP
Cisplatin	100 mg/vial (1 mg/mL)	IP
Paclitaxel	6 mg/mL	IP
Nab-Paclitaxel	100 mg/vial	IP

Study Treatment for CA224104		
Medication	**Potency**	**IP/Non-IP**
Pemetrexed	500 mg/vial	IP

Abbreviation: IP = investigational product.

Figure 1: Study Schematic



Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; AUC = area under the concentration-time curve; BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group Performance Score; EGFR = epidermal growth factor; [redacted] NSCLC = Non-small cell lung cancer; NQ = non-quantifiable; [redacted]; ORR = overall response rate; OS = overall survival; PD = progressive disease; PDCT = platinum doublet chemotherapy; [redacted] PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PRO = patient-reported outcome; Q3W = every 3 weeks; SAE = serious adverse event; SQ = squamous.

The Part 1 dose safety confirmation period is 12 weeks after the first dose. Up to approximately 120 eligible participants to enroll in the study will be randomized 1:1 to experimental Arms A or B. Nivolumab plus relatlimab, the immune checkpoint inhibitors hereon referred to as immunotherapy, will be administered in a site-and-subject blinded manner, whereas chemotherapy will be administered as open label.

Arm A: Nivolumab 360 mg Q3W + relatlimab 720 mg Q3W + 4 cycles of histology-based PDCT

Arm B: Nivolumab 360 mg Q3W + relatlimab 360 mg Q3W + 4 cycles of histology-based PDCT

During the treatment phase of Part 2 of the study, participants will receive the following treatments. Immunotherapy and chemotherapy will be administered as open-label interventions.

Arm C: Nivolumab 360 mg Q3W + relatlimab 360 mg[a] Q3W + 4 cycles of histology-based PDCT[b] or

Arm D: Nivolumab 360 mg Q3W + 4 cycles of histology-based PDCT[b]

[a] The relatlimab dose to be included in Arm C will be determined by the outcome of the dose safety confirmation that will take place in Part 1 of the study and other benefit-risk considerations at asset level. This was determined to be relatlimab 360 mg.

[b] Histology-based PDCT will be as follows:

NSQ: Carboplatin area under the concentration-time curve (AUC) 5 or 6* or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (maintenance permitted)

SQ: Carboplatin AUC 6 + paclitaxel 200 mg/m^2 or nab-paclitaxel 100 mg/m^2

Note: Carboplatin AUC 6 for NSQ and nab-paclitaxel for SQ histology is permitted only in Part 1.

[redacted]

Dose reductions are not permitted for immunotherapy.

All participants will be treated until progression, presence of intolerable toxicities, withdrawal of consent, or study end, whichever comes first. Continuous safety evaluations and tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Participants will be allowed to continue study treatment until the first occurrence of any of the following situations:

- Progressive disease defined by RECIST v1.1 unless participants meet criteria for treatment beyond progression.
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to therapy.
- Participant meets criteria for discontinuation of study treatment.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for Study CA224104 during the open-label Part 2 phase. The independent DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The independent DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for nivolumab/relatlimab. The independent DMC will act in an advisory capacity to BMS and will monitor participant safety data for Part 2 of the study.

BMS will have responsibility for the overall conduct of the study, including managing the communication of study data. BMS will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Details of the independent DMC responsibilities and procedures will be specified in the DMC charter.

In addition to the DMC, a safety committee (SC) consisting of BMS research and development representatives (including clinical development, drug safety, and statistics) and external representatives (including a selection of the study investigators) will regularly meet to evaluate the accumulating safety data of participants on the dose safety confirmation portion of the study (Part 1) and provide input to interpret safety signals. Information reviewed at each time point may include disposition, demographics, AEs, TRAEs, TRAEs leading to discontinuation, exposure, death data, and any other data deemed relevant (laboratory, pathology, autopsy reports, physical descriptions). The minutes of these meetings will be documented in the Trial Master File. The SC will not share responsibilities with the DMC (ie, the SC is responsible for monitoring Part 1 and the DMC for Part 2). Decisions on safety, toxicity, and benefit-risk regarding each dose level will be solely the responsibility of BMS and will take account of the totality of the data available.

Although the SC will meet only during Part 1 of the study, the safety of the selected dose will continue to be monitored in Part 2. The DMC will regularly review any potential emergent safety signal that was not observed in Part 1 (note that the DMC will receive the most recent Part 1 safety data as well.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA224104)

Procedure	[redacted]	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed prior to randomization.
Medical History	X	Including disease state related to the study, stage, histology, mutation status, prior therapies for advanced disease, and other relevant history.
Safety Assessments		
Physical Measurements/ PE	X	Full PE. Include height and weight. Within 14 days prior to randomization.
ECOG Performance Status	X	See Appendix 7. Within 14 days prior to randomization.
Vital Signs	X	Oxygen saturation, BP, heart rate, and temperature. Obtain at the screening visit, within 14 days prior to randomization.
Assessment of Baseline Signs and Symptoms	X	Within 14 days prior to randomization.
AE/SAE Assessments	X	Collected from time of consent. All AEs/SAEs must be graded per CTCAE v5. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Concomitant Medication Collection	X	Within 14 days prior to randomization through the study treatment period. Document vaccine use within 30 days prior to randomization. See Section 7.7.
Pregnancy Test (WOCBP only) FSH	X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done at Screening in WOCBP. Negative pregnancy test required at Screening (an extension up to 72 hours prior to start of study drug may be permissible in situations where results cannot be obtained within the standard 24-hour window). FSH screening - only required to confirm menopause in women < 55 years of age.

Table 2-1: Screening Procedural Outline (CA224104)

Procedure	[redacted]	Notes
Laboratory Assessments		
Laboratory Tests	X	Must be performed within 14 days prior to randomization. See Table 9.4.5-1 for list.
[redacted]	X	Within 14 days prior to randomization.
ECG (12-lead)	X	At rest. Within 14 days prior to randomization. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Echocardiogram	X	LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE is preferred test) within 6 months before date of first dose. Participants with other significant abnormalities on ECHO/MUGA should be discussed with the BMS MM prior to enrollment.
Efficacy Assessments		
Body Imaging	X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, [redacted] prior to randomization. See Section 9.1.1.1 for further details.
Brain Imaging	X	MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out brain metastases, [redacted] prior to randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.

Table 2-1: Screening Procedural Outline (CA224104)

Procedure	[redacted]	Notes
Biomarker Assessments		
Tumor Tissue (Biomarkers)	X	[redacted]
EGFR, ALK, and ROS-1, BRAF V600E Mutation Status	X	EGFR, ALK, and ROS-1 results required for all nonsquamous participants prior to randomization. Historical results obtained as standard of care prior to screening period are acceptable. EGFR mutation, ALK, and ROS-1 tests should be performed by site (preferred) or by central laboratory. The use of FDA-approved or local Health Authority-approved tests for EGFR and ALK are strongly encouraged. Central laboratory will require additional tissue for central testing if not performed locally (see Laboratory Manual). • EGFR mutation test (tumor tissue or blood) will be performed using PCR-based assay or next generation sequencing. Tests other than PCR or next generation sequencing will be requested to repeat using PCR or next generation sequencing-based methods. • ALK and ROS-1 rearrangement tests are mandatory for participants with nonsquamous histology. Participants with known ALK/ROS-1 translocations which are sensitive to available targeted inhibitor therapy are excluded. • If known status of BRAF V600E mutations (which are sensitive to available targeted inhibitor, therapy), participant is excluded. If BRAF mutation status is unknown or indeterminate, participant may enroll.

Table 2-1: Screening Procedural Outline (CA224104)

Procedure	[redacted]	Notes
IRT/Clinical Drug Supplies		
IRT	X	For participant number assignment at the time informed consent is obtained.
Outcomes Assessments		
[redacted]	X	Part 2 only. Within 14 days prior to randomization.
PGIS	X	Part 2 only. Within 14 days prior to randomization.
[redacted]	X	Part 2 only. Within 14 days prior to randomization.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; BP = blood pressure; BRAF = B- proto-oncogene; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; [redacted] FSH = follicle-stimulating hormone; HCG = human chorionic gonadotropin; IRT = Interactive Response Technology; [redacted] LVEF = left ventricular ejection fraction; MM = Medical Monitor; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; [redacted] NSQ = non-squamous; PCR = polymerase chain reaction; PE = physical examination; PGIS = Patient Global Impression of Severity; [redacted] SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = squamous; TTE = transthoracic echocardiogram; WOCBP = women of childbearing potential.

Table 2-2: On Treatment Procedural Outline (CA224104)

Procedure	[redacted]		
Safety Assessments			
Targeted Physical Examination and ECOG Performance Status	X	X	[redacted] Confirm ECOG status on C1D1 and each subsequent cycle. See Appendix 7.
Physical Measurements	X	X	
Vital Signs	X	X	Including oxygen saturation, BP, heart rate, and temperature.
AE and SAE Assessments	Continuously during the study		All AEs (SAEs or nonserious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. SAEs to be approved in RAVE within 5 days from entry. All AEs/SAEs must be graded using CTCAE v5.
Review of Concomitant Medications	X	X	[redacted]
ECG (12-lead)	X	See note	ECG required only on [redacted] Symptom-based ECG or with [redacted] may be performed as required.
Echocardiogram	See notes		As clinically indicated or at [redacted]
Pregnancy Test (WOCBP only)	X	X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG). To be conducted within 24 hours prior to treatment.

Table 2-2: On Treatment Procedural Outline (CA224104)

Procedure	[redacted]		
Laboratory Assessments			
Laboratory Tests[redacted]	X	X	Within 72 hours prior to dosing, including hematology, serum chemistry, urinalysis, thyroid function tests, [redacted] All laboratory results should be checked prior to dosing. [redacted] Please refer to Table 9.4.5-1 Table 9.4.5-1. [redacted] Note: C1D1 labs do not need to be repeated if performed within 14 days of dosing. TSH is done every 2 cycles.

Table 2-2: On Treatment Procedural Outline (CA224104)

Procedure	[redacted]		
[redacted]	X* (See Notes)	X* (See notes)	[redacted] * For C1D1, value taken at screening (pre-randomization) may be used and need not be repeated All results should be checked as soon as possible. Symptom-based [redacted] may be performed as clinically indicated, thereafter. For [redacted] please refer to the IMAE [redacted]
Clinical Observations	See Notes		All participants should be clinically evaluated for any immune-mediated events. Evaluations should occur every week up to and [redacted] Participants with any clinical symptoms should immediately be evaluated. For non-dosing visits, assessments may be performed remotely by the Investigator/delegate.
[redacted]			
Efficacy Assessments			
Body Imaging	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks starting from date of randomization (± 7 days) until [redacted] (± 7 days) beginning on Week 49. Imaging should continue until BICR disease progression or treatment discontinuation (whichever occurs later), participant withdrawal of consent, or death. See Section 9.1.1.1 for further details.		
Brain Imaging	Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) study per standard of care [redacted] or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.		

Table 2-2: On Treatment Procedural Outline (CA224104)

Procedure	[redacted]		
PK and Immunogenicity Assessments			
PK Samples	Throughout the study		See Section 9.5.
Immunogenicity Samples	Throughout the study		See Section 9.5.
Outcomes Assessments			
[redacted]	X	See note	Completed prior to dosing on Day 1 of each cycle from Cycle 1 through Cycle 10 and then every other cycle until cycle 36. Part 2 only: Completed every 6 cycles from Cycle 36 until the end of the treatment period.
[redacted]	X	See note	
PGIS	X	See note	
[redacted]	X	See note	
PGIC		See note	Completed prior to dosing on Day 1 of each cycle from Cycle 2 through Cycle 10 and then every other cycle until Cycle 36. Part 2 only: Completed every 6 cycles from Cycle 36 until the end of the treatment period. The PGIC is not administered on C1D1
Clinical Drug Supply			
IRT Vial Assignment	X	X	Within 1 day prior to dosing.
Study Treatment[b,c]			
Part 1: Dose Safety Confirmation: Nivolumab + Relatlimab + PDCT Q3W × 4	X	X	Arm A[e]: Nivolumab 360 mg Q3W + Relatlimab 720 mg Q3W+ 4 cycles of PDCT Q3W Arm B[e]: Nivolumab 360 mg Q3W + Relatlimab 360 mg Q3W+ 4 cycles of PDCT Q3W
Part 2: Nivolumab + Relatlimab + PDCT Q3W × 4 Nivolumab + PDCT Q3W × 4	X	X	Arm C[d,e]: Nivolumab 360 mg Q3W + Relatlimab 360 mg Q3W+ 4 cycles of PDCT Q3W Arm D: Nivolumab 360 mg Q3W + 4 cycles of PDCT Q3W

Abbreviations: AE = adverse event; [redacted] BICR = blinded independent central review; BP = blood pressure; C = Cycle; [redacted] CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; [redacted] HCG = human chorionic gonadotropin; Ig = immunoglobulin; IRT = Interactive Response Technology; [redacted] MRI = magnetic resonance imaging; [redacted] NSQ = non-squamous; PDCT = platinum doublet chemotherapy; PGIC = Participant Global Impression of Change; PGIS = Participant Global Impression of Severity; PK = pharmacokinetics; [redacted] Q3W = every 3 weeks; RAVE EDC = Electronic Data Capture; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSH = thyroid-stimulating hormone; v = version; WOCBP = women of childbearing potential.

[redacted]

[b] Pemetrexed maintenance permitted for NSQ participants.

[c] Treat until progression, unacceptable toxicity, withdrawal of consent, or study end whichever occurs first.

[d] Relatlimab dose of 360 mg Q3W was selected for Part 2. See Section 5.5.2.

[e] [redacted]

NOTES:

1. If a dose is delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occur (except radiographic tumor assessments) and continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.
2. Supporting documents related to AE/SAE may be required via additional queries, and some of the assessments in this section may not be captured as data in eCRF. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-3: Follow-up and Survival Procedural Outline (CA224104)

Procedure	[redacted]			Notes
Safety Assessments				
Targeted Physical Examination and ECOG Performance Status	X			To assess for potential late emergent study drug-related issues. Include weight and ECOG performance status.
Vital Signs	X			Including oxygen saturation, BP, heart rate, and temperature.
AE Assessment	X		X	SAEs should be approved in RAVE within 5 days from entry. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of [redacted] following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out. All AEs/SAEs are to be graded using CTCAE v5.
Review of Concomitant Medications	X			
Laboratory Tests	X			Required at Follow-up Visit 1. Repeat at Follow-up Visit 2 only if study drug-related toxicity persists. Please refer to Table 9.4.5-1 Table 9.4.5-1.
Pregnancy Test (WOCBP only)	X		See notes	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) pregnancy testing is only required at Follow-up Visits 1 and 2, unless increased frequency and duration is required per local regulations.
Efficacy Assessments				
Body Imaging		X		For participants who have not experienced BICR-confirmed PD radiographic assessments, or who discontinue study

Table 2-3: Follow-up and Survival Procedural Outline (CA224104)

Procedure	[redacted]			Notes
				treatments for reasons other than PD, contrast-enhanced CT of the chest and CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should continue Q6W (± 7 days) starting from date of randomization (± 7 days) until [redacted] (± 7 days) beginning on Week 49 until BICR disease progression or treatment discontinuation (whichever occurs later), participant withdrawal of consent, or death. See Section 9.1.1.1 for further details.
Brain Imaging		X		Participants with a history of brain metastasis or symptoms should have surveillance MRIs (without and with contrast) per standard of care [redacted] or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.
Collection of Survival Status and Subsequent Therapy Information	X		X	Collect [redacted] in Survival Visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after second-line therapy will be collected.
Subsequent Progression (PFS-2)	X		X	For participants who start subsequent anti-cancer therapy, subsequent PD date and diagnosis method during subsequent treatment will be recorded on the eCRF during the Follow-up Period.
PK Assessments				
Collection of PK and Immunogenicity Samples	X			See Section 9.5.

Table 2-3: Follow-up and Survival Procedural Outline (CA224104)

Procedure	[redacted]			Notes
Outcomes Assessments				
[redacted]	X			
	X			
	X			
PGIS	X			
PGIC	X			

Abbreviations: AE = adverse event; BICR = blinded independent central review; BP = blood pressure; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; [redacted] HCG = human chorionic gonadotropin; Ig = immunoglobulin; MRI = magnetic resonance imaging; [redacted] PD = progressive disease; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; [redacted] RAVE EDC = Electronic Data Capture; Q6W = every 6 weeks; [redacted] SAE = serious adverse event; v = version; WOCBP = women of childbearing potential.

[redacted]

Note: In the event multiple procedures are required at a single time point clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the PK samples can be collected on time.

3 INTRODUCTION

Study CA224104 is a Phase 2, randomized study that will evaluate nivolumab plus relatlimab in combination with platinum-based chemotherapy, versus nivolumab plus platinum-based chemotherapy in participants with previously untreated, Stage IV or recurrent non-small cell lung cancer (NSCLC). The study will take place in 2 parts: a site- and subject-blinded dose safety confirmation (Part 1) and an open-label randomized study (Part 2).

Immunotherapeutic approaches have recently demonstrated clinical efficacy in several cancer types, including NSCLC.[1] Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands.

Nivolumab (BMS-936558) is a fully human, immunoglobulin (Ig) G4 (kappa) isotype monoclonal antibody that binds the programmed cell death protein 1 (PD-1) receptor on activated immune cells and disrupts engagement of the receptor with its ligands programmed death-ligand 1 (PD-L1) (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[2] (See Section 3.2.1 for more details on the mechanism of action of nivolumab.)

Relatlimab (BMS-986016) is a fully human lymphocyte-activation gene 3 (LAG-3) specific antibody that was isolated following immunization of transgenic mice expressing human Ig genes. Relatlimab binds to LAG-3 receptors expressed on T-cells with high affinity and prevents binding of this receptor to cells bearing its ligands, major histocompatibility complex (MHC) Class II and fibrinogen-like protein 1 (FGL-1).[3,4] Relatlimab binding inhibits the negative regulatory function of LAG-3 mediated through its interaction with ligands in vitro. By blocking the normal down-regulatory 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) agents. Dual checkpoint inhibition with relatlimab and nivolumab results in enhanced T-cell effector function that is greater than the effects of either antibody alone in murine syngeneic tumor models.[5] (See Section 3.2.2 for more background on the mechanism of action of relatlimab.)

The objective of the CA224104 study will be to confirm the safety profile of nivolumab plus relatlimab in combination with platinum doublet chemotherapy (PDCT) and to determine if this novel combination improves overall response rate (ORR) in participants with previously untreated Stage IV or recurrent NSCLC when compared with nivolumab plus histology-based PDCT. This study is expected to provide initial, proof of concept evidence of the selected target dose for development of relatlimab in combination with nivolumab and PDCT in first line (1L) NSCLC. The use of nivolumab in combination with PDCT as a control arm will aid in establishing the contribution of the individual immunotherapy components to the synergistic/additive effect of the relatlimab and nivolumab combination.

3.1 Study Rationale

Nivolumab, relatlimab, and PDCT each have non-overlapping anti-cancer mechanisms and may have synergistic and/or additive activity as combination therapy, with few overlapping toxicities. LAG-3 is often expressed on chronically exhausted T-cells and is frequently co-expressed with PD-L1 on tolerized tumor-infiltrating lymphocytes (TILs) across tumor types.[6,7,8] The rationale for combining a LAG-3 inhibitor and an anti–PD-1/PD-L1 agent originates from evidence suggesting that LAG-3 has a potential role in T-regulatory cell (Treg) suppression and anti–PD-1 resistance.[9]

The current standard of care, anti-PD-(L)1 (± anti- cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) in combination with PDCT has demonstrated significant improvement in overall survival (OS) as well as PFS in participants with previously untreated metastatic NSCLC.[10,11,12,13,14] In the CA224020 Phase 1/2a study, the combination of nivolumab and relatlimab demonstrated tolerability, peripheral T-cell activation, and preliminary clinical activity of the combination of nivolumab and relatlimab in advanced melanoma participants who had been previously treated with anti-PD-1/PD-L1 therapy.[15,16] Additionally, data from a Mar-2020 database lock of CA224020 Part C showed activity in metastatic or recurrent NSCLC in an immunotherapy-naive population as well as in relapsed and refractory subgroups that were previously treated with immunotherapy (see Section 3.2.4).[17] These data indicate the potential of nivolumab plus relatlimab and chemotherapy to improve on the activity shown by anti-PD-(L)1 in combination with chemotherapy.

There are several candidate biomarkers which may help select participants who will benefit from the addition of relatlimab to nivolumab plus chemotherapy. Multiple clinical trials have established the correlation between PD-L1 expression and increased response to PD-1 and PD-L1 immune checkpoint inhibition. Data from CA224020 demonstrated preliminary evidence that participants with LAG-3 expression are more likely to respond to treatment with relatlimab in combination with nivolumab.[17] Recently, FGL-1 was identified as a new ligand for LAG-3 that is responsible for its T-cell inhibitory function and potentially a new mechanism for immuno-evasion.[4] Therefore, FGL-1 may be a novel biomarker to predict outcomes of anti-PD-1 and anti-LAG-3 tumor therapies. Tumor model studies using FGL1-KO mice demonstrate that FGL1 has a potent immune suppressive effect on anti-tumor immunity that is dependent on LAG-3. Moreover, FGL1 may be a potential biomarker to predict the outcome of anti-PD therapy, since high plasma FGL1 levels are associated with a worse response to anti-PD therapy in NSCLC and melanoma participants.

The benefit of the relatlimab plus nivolumab combination continues to be explored in several types of metastatic malignancies. The combination of nivolumab 360 mg every 3 weeks (Q3W) plus relatlimab 720 mg or 360 mg Q3W and 4 cycles of PDCT is expected to have a synergistic effect in the 1L NSCLC population based on the clinical activity shown by the 2 individual combinations (nivolumab plus relatlimab and nivolumab plus PDCT) and their distinct but complementary mechanisms of action. For more information on the rationale for the combination of nivolumab

and relatlimab plus PDCT and the dosing choices for this study, see Sections 3.2.3, [redacted] 5.5.1, and 5.5.2.

3.1.1 Research Hypothesis

The hypotheses of Study CA224104 are as follows:

- Part 1 (Dose safety confirmation): Nivolumab, 360 mg, plus relatlimab, 720 mg or 360 mg, Q3W combined with 4 cycles of PDCT is safe in participants with 1L Stage IV or recurrent NSCLC.
- Part 2: Nivolumab plus relatlimab combined with 4 cycles of PDCT improves ORR when compared to nivolumab plus PDCT in participants with 1L Stage IV or recurrent NSCLC.

3.2 Background

NSCLC remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[18] Until recently, the treatment of participants with advanced NSCLC whose tumors did not have a targetable genetic alteration was cytotoxic chemotherapy alone. In spite of treatment, participants with metastatic NSCLC treated with PDCT had a median survival of approximately 10 months and a 5-year survival rate of less than 5%. The introduction of immune checkpoint inhibitors targeting the PD-1 signaling pathway in the treatment of participants with NSCLC has had a significant effect on participant survival. Pembrolizumab combined with chemotherapy in the front-line setting has demonstrated an improvement in OS in NSCLC participants as compared to chemotherapy alone.[10,11] More recently, nivolumab plus ipilimumab, and nivolumab plus ipilimumab in combination with chemotherapy, also showed benefit over chemotherapy in this setting.[13,14] However, despite these advances, the median survival of 1L participants with metastatic NSCLC is approximately 22 months in the non-squamous (NSQ), and 15.9 months in the squamous (SQ) population.[11,19]

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies as described in the Investigator's Brochure (IB). The efficacy of the nivolumab plus PDCT combination is well characterized as it has been studied extensively in NSCLC (CA209012, CA209227, ONO-4538-04, and CA209568/CA2099LA [nivolumab + ipilimumab + PDCT]). Results from these studies suggest that the addition of platinum-based chemotherapy to anti–PD-1 treatment can improve outcomes in an unselected participant population and that the regimen is well tolerated.[20] The combination of nivolumab plus chemotherapy was first studied in the Phase 1 CA209012 study. Results supported additional development of the combination, with the nivolumab plus pemetrexed/cisplatin arm reporting an 18-month OS rate of 60% (see Section 3.2.3). In Part 2 of the Phase 3 CA209227 1L NSCLC study evaluating nivolumab in combination with PDCT vs PDCT, even though the primary endpoint of OS in the NSQ population did not reach statistical significance, the combination of nivolumab plus chemotherapy exhibited encouraging activity across histologies, regardless of PD-L1 expression. The median PFS and OS were numerically higher in participants who received nivolumab plus chemotherapy with a median

OS of 18.27 months vs 14.72 months in the chemotherapy group, and a median PFS of 8.38 months with the nivolumab combination vs 5.52 months in the control arm.

In addition, dual immunotherapy in combination with PDCT has been shown to improve efficacy outcomes reported by the combination of anti-PD-1 plus chemotherapy with a manageable safety profile. With a minimum follow-up of 12.7 months, Study CA2099LA, which evaluated nivolumab plus ipilimumab in combination with PDCT vs PDCT in a similar population of 1L NSCLC participants, reported a median PFS of 6.7 months (5.6 to 7.8).[14] The combination of nivolumab and ipilimumab plus 2 cycles of PDCT demonstrated a survival benefit vs chemotherapy alone with a hazard ratio (HR) for death of 0.66 (0.55 to 0.80). This benefit was evident across histologies (SQ OS HR = 0.62 and NSQ OS HR = 0.69) and regardless of PD-L1 expression. No new safety signals or toxicities were identified with nivolumab plus ipilimumab in combination with PDCT relative to each agent as a monotherapy or in combination.

Beyond these now well-studied combinations, preclinical and clinical data have generated promising results for the anti-LAG-3 agent relatlimab. In Phase 1/2a Study CA224020 evaluating the combination of relatlimab with nivolumab, evidence of clinical activity was preliminarily observed across 6 immunotherapy-naive expansion cohorts including NSCLC (see Section 3.2.4). In addition, preclinical data suggest that dual anti-LAG-3/PD-1 immunotherapy promotes tumor-specific responses and could therefore be less toxic than CTLA-4 blockade.[9] For these reasons, it is hypothesized that the combination of nivolumab plus relatlimab and PDCT may aid in controlling disease progression through a synergistic effect while maintaining an acceptable safety profile. Information regarding the choice of control arm can be found in Section 5.4.5.

The aim of this randomized Phase 2 study is to confirm the safety profile of nivolumab plus relatlimab in combination with PDCT and to determine if nivolumab plus relatlimab in combination with PDCT improves ORR when compared to nivolumab plus PDCT in participants with previously untreated Stage IV or recurrent NSCLC.

3.2.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[21,22,23] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[24] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, inducible T-cell co-stimulator (ICOS), and T-lymphocyte attenuator (BTLA).[25] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-γ (IFN-γ), and Bcl-xL. PD-1 expression also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[26] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen-specific recall response indicates that nivolumab-augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[27]

3.2.2 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human Ig genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC Class II (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3–mediated inhibition of an antigen-specific murine T-cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, relatlimab enhances activation of human T-cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody).

See also the IB for relatlimab Section 4.1 (Nonclinical Pharmacology Studies with Relatlimab) and Section 4.2 (Nonclinical Pharmacokinetics with Relatlimab).

3.2.3 Nivolumab plus PDCT Clinical Activity

In CA209012, a multi-arm Phase 1 safety study of nivolumab in chemotherapy-naive NSCLC, 56 subjects were administered nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, or carboplatin/paclitaxel. Overall response rate (ORR) with the different combinations ranged from 42% to 50%.

Nivolumab in combination with chemotherapy was more recently studied in Part 2 of Phase 3 trial CA209227.[20] A summary of the efficacy results presented at European Society for Medical Oncology (ESMO) I-O 2019 is shown in Table 3.2.3-1.

Table 3.2.3-1: CA209227 Part 2 - Efficacy Outcomes with Nivolumab + Chemotherapy vs Chemotherapy

	NSQ		SQ		All Randomized	
	Nivo + Chemo n = 270	**Chemo n = 273**	**Nivo + Chemo n = 107**	**Chemo n = 105**	**Nivo + chemo n = 377**	**Chemo n = 378**
OS						
Events, n%	156 (57.8)	164 (60.1)	68 (63.6)	75 (71.4)	224 (59.4)	239 (63.2)
Median, mo	18.8	15.6	18.3	12.0	18.3	14.7
HR (95% CI)	0.86 (0.69-1.08)[a] P = 0.1859		0.69 (0.50-0.97)		0.81 (0.67-0.97)	
12-mo OS rate, %	67.3	59.2	66.1	48.5	66.9	56.2
PFS						
Events, n(%)	187 (69.3)	200 (73.3)	79 (73.8)	82 (78.1)	266 (70.6)	282 (74.6)
Median, mo	8.7	5.8	7.1	4.4	8.4	5.5
HR (95% CI)	0.67 (0.55-0.82)		0.51 (0.37-0.70)		0.62 (0.52-0.73)	
12-mo PFS rate, %	39.5	25.7	31.7	9.3	37.3	21.3
ORR, n (%)	130 (48.1)	80 (29.3)	64 (59.8)	34 (32.4)	194 (51.5)	114 (30.2)

Abbreviations: CI = confidence interval; HR = hazard ratio; n = number of subjects; NSQ = non-squamous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SQ = squamous.

[a] 95.62% CI.

Due to the hierarchical nature of the statistical design of CA209227, the fact that the primary endpoint of OS in the NSQ population was not statistically significant rendered additional endpoints purely descriptive. However, it is important to note that ORR, PFS, and OS all demonstrated a trend towards improved efficacy with the nivolumab plus chemotherapy combination versus chemotherapy alone after a minimum follow-up of 19.5 months for OS and 18.4 months for all other data. The OS HR in all randomized subjects was 0.81 (95.62% confidence interval [CI]: 0.67, 0.97). The median PFS and OS were numerically higher in participants who received nivolumab plus chemotherapy, with a median OS of 18.27 months vs 14.72 months in the chemotherapy group, and a median PFS of 8.38 months with the nivolumab combination vs 5.52 months in the control arm. In addition, ORR was higher with nivolumab plus chemotherapy when compared to chemotherapy alone in the all randomized population, as well as in the NSQ participants (48.1% vs 25.7%) and the SQ participant sub-group (59.8% vs 32.4%).

3.2.4 Relatlimab Preclinical and Clinical Activity

LAG-3 has been shown to be expressed in TILs of several tumor types, including breast, ovarian, and lung cancers, often in connection with increased PD-1+ T-cells.[28] Preclinical data presented in recent years illustrate a clear synergy between the inhibitory receptors LAG-3 and PD-1 in controlling immune homeostasis, preventing autoimmunity, and enforcing tumor-induced tolerance.[29] Importantly, dual antibody-treated mice showed more robust immune responses than either single-treated group in these studies, and analyses of mutant mice revealed a cooperative requirement for LAG-3 and PD-1 in maintaining immune homeostasis.

The single-agent anti-tumor activity of anti-LAG-3 antibody (19C7) was evaluated in the very immunogenic Sa1N fibrosarcoma tumor model.[30] As compared to the isotype control group, all doses between 1 and 30 mg/kg of anti-LAG-3 clone 19C7 demonstrated anti-tumor efficacy, leading to between 30% and 60% of the mice being rendered tumor free at the end of study.

Combined anti-PD-1 and anti-LAG-3 activity was also assessed in the Sa1N model. In 2 different studies, anti-LAG-3 antibody, C9B7W, inhibited the growth of Sa1N tumors in mice when administered as monotherapy and when combined with anti-PD-1 antibody, 4H2.[31,32] The combination of these 2 antibodies resulted in 80% to 90% tumor-free mice and reductions in median tumor volumes superior to that of anti-PD-1 or anti-LAG-3 antibody monotherapy alone.

Relatlimab is being investigated, alone and in combination with other treatments, in several types of cancer. As a single therapy, relatlimab demonstrated activity in hematologic malignancies. In the Phase 1/2a Study CA224022 evaluating relatlimab monotherapy in relapsed or refractory hematologic B-cell malignancies, objective responses were observed in subjects with marginal zone lymphoma, Hodgkin lymphoma, and mantle cell lymphoma.[5]

Phase 1/2a Study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab with and without nivolumab to treat various solid tumors. Initial results published in 2017 at the American Society for Clinical Oncology (ASCO) and ESMO annual meetings, show synergistic activity when relatlimab is combined with nivolumab in solid tumors.[15,16] Part C of the study demonstrated preliminary proof-of-concept efficacy in the combination treatment expansion cohort of advanced melanoma with prior anti-PD-(L)1 treatment. [redacted]

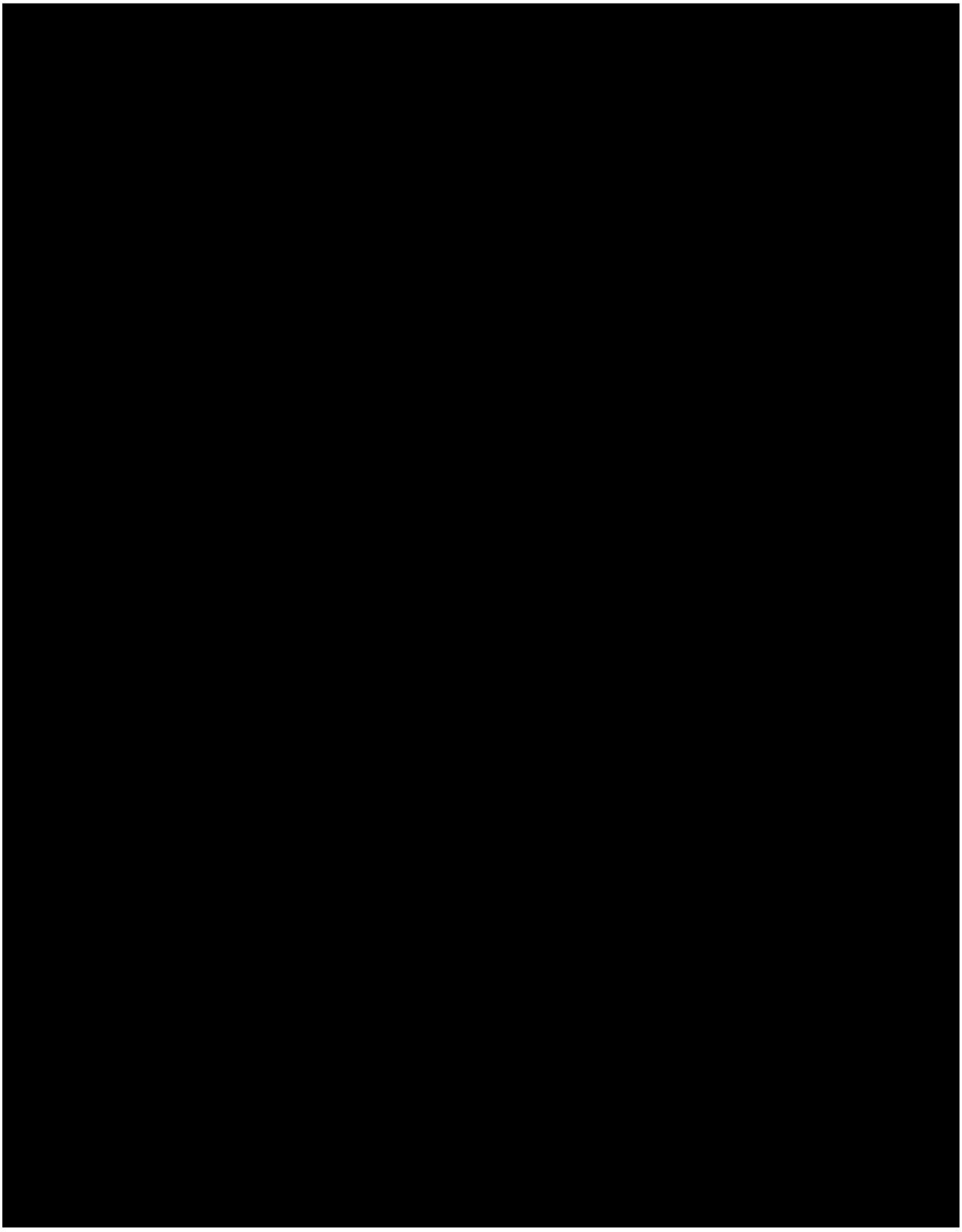
[redacted]

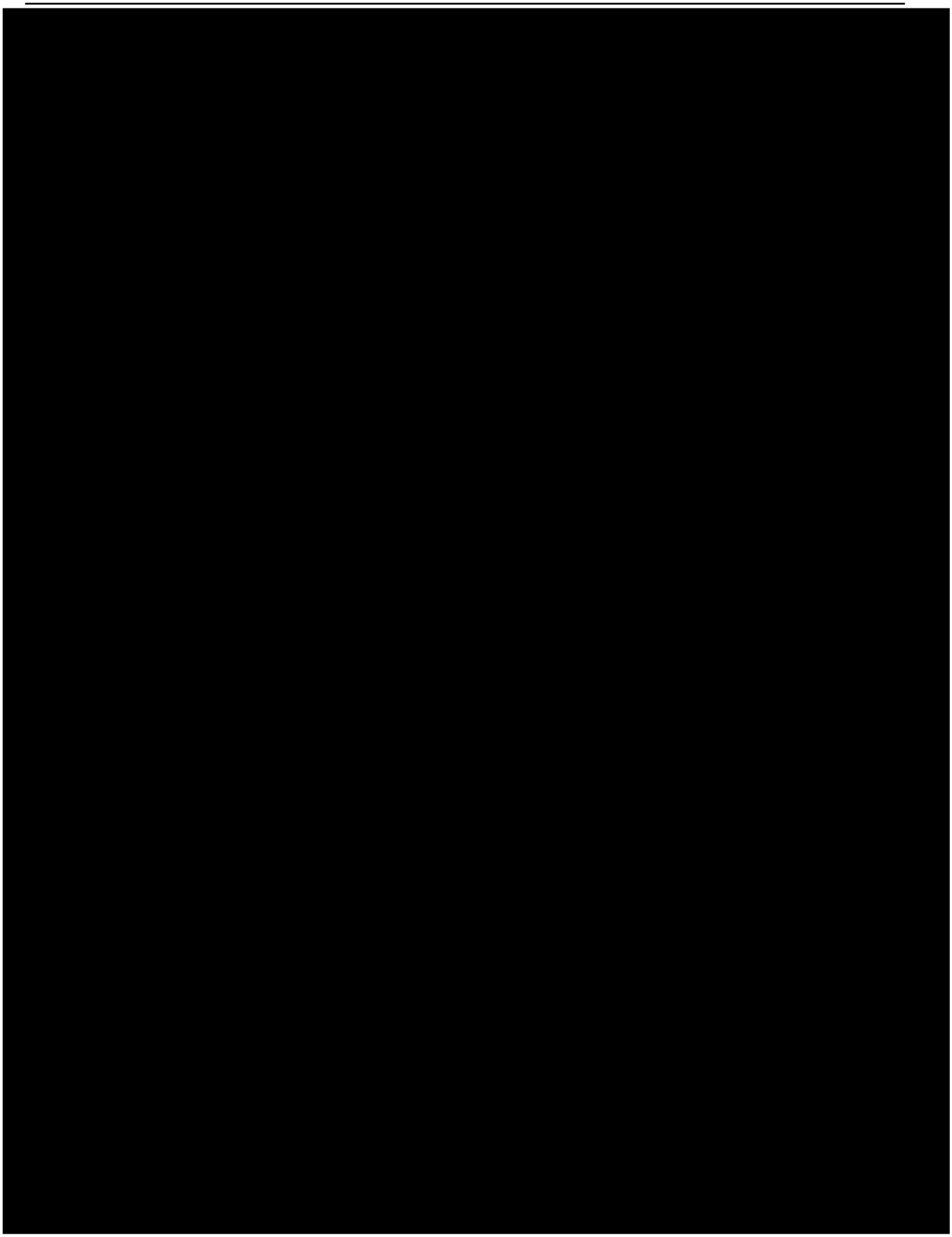
3.2.5 Relatlimab Monotherapy Safety

The safety profile of relatlimab appears manageable in the 3 ongoing studies with relatlimab monotherapy [redacted] with no maximum tolerated dose (MTD) reached at any dose tested up to an 800-mg flat dose every 2 weeks. [redacted]

[redacted]

[redacted]





[redacted]

3.2.7 Nivolumab Plus PDCT Safety

Nivolumab in combination with chemotherapy has been proven to be safe. In Part 2 of Study CA209227, the overall safety profile of nivolumab plus PDCT in all treated subjects with chemotherapy-naïve Stage IV or recurrent NSCLC was consistent with the established safety

profile of each component of the regimen. No new safety signals or toxicities were identified relative to previous experience with nivolumab monotherapy or with chemotherapy. Safety results for all treated participants in CA209227 Part 2 are summarized in Table 3.2.7-1.

Table 3.2.7-1: Safety Results: All treated Subjects in CA209227 Part 2

	Nivolumab + Chemotherapy N = 375		Chemotherapy N = 371	
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	195 (52.0)	142 (37.9)	131 (35.3)	100 (27.0)
Drug-related SAEs	94 (25.1)	75 (20.0)	49 (13.2)	43 (11.6)
All-causality AEs leading to DC	102 (27.2)	55 (14.7)	59 (15.9)	31 (8.4)
Drug-related AEs leading to DC	73 (19.5)	36 (9.6)	31 (8.4)	12 (3.2)
All-causality AEs	371 (98.9)	223 (59.5)	358 (96.5)	193 (52.0)
Drug-related AEs	318 (84.8)	168 (44.8)	291 (78.4)	131 (35.3)
≥ 15% drug-related AEs in any treatment group				
Anemia	122 (32.5)	39 (10.4)	117 (31.5)	43 (11.6)
Nausea	84 (22.4)	4 (1.1)	108 (29.1)	5 (1.3)
Decreased appetite	60 (16.0)	8 (2.1)	53 (14.3)	4 (1.1)
Fatigue	58 (15.5)	10 (2.7)	57 (15.4)	7 (1.9)
All-causality Select AEs				
Endocrine	45 (12.0)	3 (0.8)	7 (1.9)	0
Gastrointestinal	74 (19.7)	8 (2.1)	42 (11.3)	2 (0.5)
Hepatic	84 (22.4)	15 (4.0)	40 (10.8)	3 (0.8)
Pulmonary	25 (6.7)	7 (1.9)	1 (0.3)	1 (0.3)
Renal	56 (14.9)	6 (1.6)	39 (10.5)	3 (0.8)
Skin	100 (26.7)	8 (2.1)	43 (11.6)	3 (0.8)
Hypersensitivity/infusion reactions	22 (5.9)	2 (0.5)	8 (2.2)	1 (0.3)
Drug-related Select AEs				
Endocrine	38 (10.1)	2 (0.5)	1 (0.3)	0
Gastrointestinal	44 (11.7)	4 (1.1)	24 (6.5)	2 (0.5)
Hepatic	63 (16.8)	9 (2.4)	27 (7.3)	1 (0.3)
Pulmonary	23 (6.1)	5 (1.3)	1 (0.3)	1 (0.3)
Renal	41 (10.9)	3 (0.8)	27 (7.3)	3 (0.8)
Skin	83 (22.1)	7 (1.9)	24 (6.5)	3 (0.8)
Hypersensitivity/infusion reactions	15 (4.0)	2 (0.5)	7 (1.9)	1 (0.3)
All-causality IMAEs Within 100 Days of Last Dose Treated with Immune-modulating Medication				

Table 3.2.7-1: Safety Results: All treated Subjects in CA209227 Part 2

	Nivolumab + Chemotherapy N = 375		Chemotherapy N = 371	
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Diarrhea/colitis	14 (3.7)	5 (1.3)	1 (0.3)	1 (0.3)
Hepatitis	11 (2.9)	8 (2.1)	1 (0.3)	0
Pneumonitis	20 (5.3)	7 (1.9)	0	0
Nephritis/renal dysfunction	7 (1.9)	2 (0.5)	1 (0.3)	0
Rash	25 (6.7)	3 (0.8)	4 (1.1)	0
All-causality Endocrine IMAEs Within 100 Days of Last Dose with or without Immune-modulating Medication				
Adrenal insufficiency	2 (0.5)	1 (0.3)	0	0
Hypophysitis	1 (0.3)	1 (0.3)	0	0
All-causality OESIs Within 100 Days of Last Dose with or without Immune-modulating Medication				
Myasthenic syndrome	1 (0.3)	0	0	0
Pancreatitis	3 (0.8)	2 (0.5)	2 (0.5)	1 (0.3)
Uveitis	1 (0.3)	0	0	0
Myocarditis	3 (0.8)	3 (0.8)	2 (0.5)	0
Myositis	1 (0.3)	0	0	0

Abbreviations: AE = adverse event; CTC = common toxicity criteria DC = discontinuation; IMAEs = immune-mediated adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; OESIs = other events of special interest; SAE = serious adverse event.

MedDRA version 22.0; CTC version 4.0.

Note: All events are within 30 days of the last dose of study drug, unless otherwise indicated.

In addition, the combination of 2 immunotherapy agents, nivolumab and ipilimumab, plus chemotherapy in 1L NSCLC has also proven to be safe. In Study CA2099LA with a minimum follow-up of 12.7 months, safety results were consistent with the known safety profiles of the immunotherapy and chemotherapy components in this setting. The frequency of deaths attributed to study drug toxicity was similar in the nivolumab plus ipilimumab plus chemotherapy (2.0%) and chemotherapy (1.7%) arms. No new safety signals or toxicities were identified with nivolumab plus ipilimumab plus chemotherapy, relative to each agent as monotherapy or in combination (see Table 3.2.7-2 and Table 3.2.7-3.

Table 3.2.7-2: CA2099LA Safety Summary

	Minimal 12.7-month Follow-up			
	Nivolumab + Ipilimumab + Chemotherapy (N = 358)		Chemotherapy (N = 349)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All AEs (regardless of causality), %	356 (99.4)	245 (68.4)	342 (98.0)	188 (53.9)
Drug-related AEs, %	328 (91.6)	168 (46.9)	306 (87.7)	132 (37.8)
All AEs leading to DC, %	101 (28.2)	81 (22.6)	61 (17.5)	43 (12.3)
Drug-related AEs leading to DC, %	69 (19.3)	58 (16.2)	26 (7.4)	16 (4.6)
All SAEs, %	215 (60.1)	169 (47.2)	149 (42.7)	112 (32.1)
Drug-related SAEs, %	106 (29.6)	91 (25.4)	62 (17.8)	51 (14.6)

Abbreviations: AE = adverse event; DC = discontinuation; N = number of subjects SAE = serious adverse event.

Table 3.2.7-3: CA2099LA Drug-related Select AEs (All Treated Participants)

	Minimal 12.7-month Follow-up			
	Nivolumab + Ipilimumab +Chemotherapy (N = 358)		Chemotherapy (N = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine AE	92 (25.7)	10 (2.8)	1 (0.3)	0
Gastrointestinal AE	83 (23.2)	20 (5.6)	41 (11.7)	2 (0.6)
Hepatic AE	51 (14.2)	16 (4.5)	27 (7.7)	3 (0.9)
Hypersensitivity/infusion reaction	18 (5.0)	2 (0.6)	4 (1.1)	2 (0.6)
Pulmonary AE	19 (5.3)	6 (1.7)	4 (1.1)	1 (0.3)
Renal AE	25 (7.0)	7 (2.0)	22 (6.3)	4 (1.1)
Skin AE	145 (40.5)	16 (4.5)	28 (8.0)	1 (0.3)

Abbreviation: AE = adverse event; N = number of subjects.

3.3 Benefit/Risk Assessment

As described in Section 3.2.3, preclinical studies demonstrated that combination blockade of PD-1 and LAG-3 can induce immune activation and associated tumor rejection in fibrosarcoma and colorectal cancer models in mice. In vivo studies in murine cancer models have shown that when expressed at high levels, concomitant LAG-3/PD-1 expression is mostly restricted to TILs. This may signify that a combination immunotherapy targeting these 2 molecules may encourage

tumor-specific responses, avoiding non-specific or self-antigen-specific immune responses, potentially rendering such treatment less toxic than CTLA-4 blockade.[9]

Preliminary proof-of-concept efficacy has been demonstrated in Study CA224020, where combination dosing of relatlimab [redacted] plus nivolumab [redacted] showed the capacity to induce responses in previously heavily treated advanced solid tumors, with the added ability to trigger responses in tumors that have demonstrated resistance to anti-PD-(L)1 therapy. In this study, efficacy data in pretreated immunotherapy-naive NSCLC subjects are compelling, with similar ORR, DoR, and preliminary OS that is comparable to outcomes of chemotherapy alone in such populations. This indicates the potential of nivolumab plus relatlimab and chemotherapy to improve on the activity shown by anti-PD-1 in combination with chemotherapy (see Section 3.2.4). The addition of nivolumab to chemotherapy has shown activity in Study CA209227 demonstrating improved OS and ORR versus chemotherapy alone. In addition, improved OS has been demonstrated by combining 2 immunotherapies, nivolumab and ipilimumab, with platinum-based chemotherapy in Study CA2099LA.

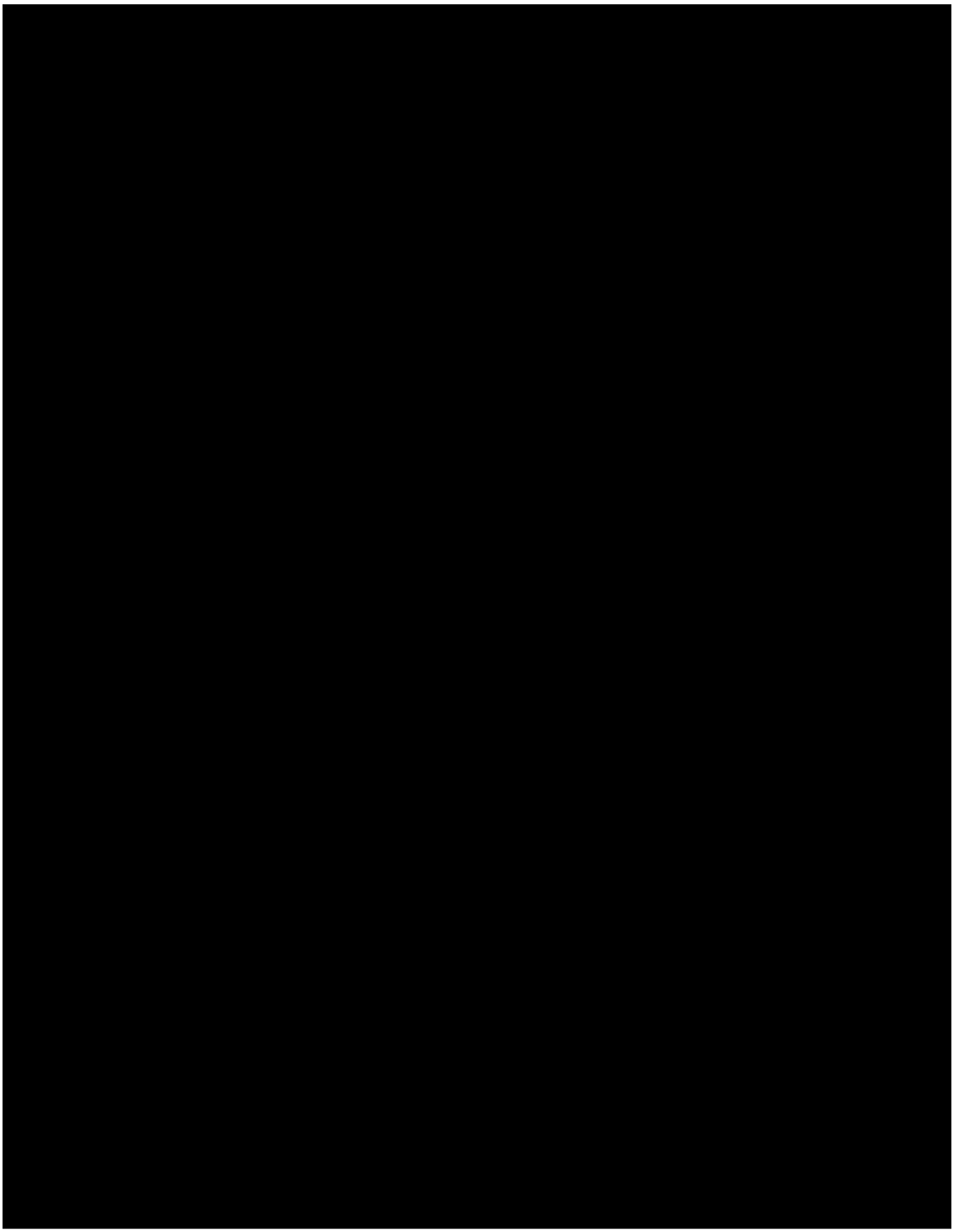
Overall, the safety profile of nivolumab in combination with relatlimab is manageable and generally consistent across the program's ongoing clinical trials, with no MTD reached at any dose tested up to [redacted] of nivolumab and [redacted] of relatlimab administered [redacted] Most AEs reported are low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. The safety profile of nivolumab in combination with chemotherapy in CA209227 was also acceptable and consistent with the safety profile of each individual component, and it was manageable using the AE [redacted] previously established for nivolumab. The combination of 2 immunotherapies, nivolumab and ipilimumab, with PDCT in CA2099LA also demonstrated acceptable safety in 1L NSCLC, with no new safety signals or toxicities identified. In both CA209227 and CA2099LA, across all AE categories (SAEs, AEs leading to discontinuation of study drug, AEs), all-causality and drug-related events were higher with the immunotherapy plus chemotherapy treatment combination when compared to chemotherapy treatment alone. See Section 3.2.7.

The agents to be used in the study have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either immune checkpoint inhibitor as monotherapy or in combination with each other or with chemotherapy, across multiple tumor types. While the combination of relatlimab, nivolumab, and platinum-based chemotherapy has not been previously evaluated in NSCLC, relatlimab and nivolumab combined with oxaliplatin-based chemotherapy is currently being assessed in gastric or gastroesophageal junction adenocarcinoma in Study CA224060.[33] After a database lock in Apr-2020 to inform the Data Monitoring Committee (DMC), the recommendation was to continue the study without any modification during a meeting held on 08-Jun-2020. Preliminary results for Study CA224060, as of database lock date 19-Nov-2020, are now available. Even though there were differences in the treatment discontinuations and SAEs regardless of causality in the RNC arm, IMAEs were not increased. These safety data are not considered to represent a change to the overall risk-benefit profile for the relatlimab development program.

[redacted]

A pattern of immune-related AEs has been defined, for which [redacted] have been developed; these are provided in [redacted] Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

[redacted]



[redacted]

Additional details on the safety profile of nivolumab and relatlimab, including results from other clinical studies, are also available in the nivolumab and relatlimab IBs.

COVID-19 Vaccines

BMS has given consideration regarding the benefit/risk of COVID-19 vaccination during participation in BMS-986016 (relatlimab) and BMS-936558 (nivolumab) clinical trials. Based on the review of current available data and evidence to date, knowledge of the mechanisms of action of the COVID-19 vaccines and Relatlimab and Nivolumab IMP, a biological or pharmacological interaction occurring between the vaccine and the IMP that would negatively impact the benefit/risk for participants in BMS relatlimab and nivolumab clinical trials is not expected; however, data will continue to be reviewed. Therefore, at this time, a COVID-19 vaccine given to participants in this trial is considered a concomitant medication with no interaction.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Part 1: Dose Safety Confirmation	
Primary	
To evaluate the proportion of participants with TRAEs leading to discontinuation within 12 weeks after the first dose of nivolumab plus 2 different dose levels of relatlimab (360 mg and 720 mg) in combination with PDCT in dose-safety evaluable participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• TRAEs leading to discontinuation within 12 weeks after the first dose
Secondary	
To evaluate the safety and tolerability of nivolumab plus 2 different doses of relatlimab (360 mg and 720 mg) in combination with PDCT in all participants with histologically confirmed 1L Stage IV or recurrent NSCLC that were treated during the dose safety confirmation period	• Incidence of TRAEs leading to discontinuation, AEs, SAEs, and select AEs
Exploratory	
To evaluate the efficacy of nivolumab plus 2 different doses of relatlimab (360 mg and 720 mg) in combination with PDCT in all randomized participants with	• ORR per RECIST v1.1 by BICR

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
histologically confirmed 1L Stage IV or recurrent NSCLC randomized in the dose safety confirmation period	
[redacted]	
To characterize the immunogenic potential of relatlimab and nivolumab in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• Anti-relatlimab and anti-nivolumab antibodies and their relationship with other outcome measures
To characterize PK of relatlimab and nivolumab in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• PK measurements of relatlimab and nivolumab
To characterize participant perceptions of the bothersomeness of the side effects of treatment in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• Proportion of participants experiencing bother [redacted]
[redacted]	
Part 2	
Primary	
To evaluate ORR of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• ORR per RECIST v1.1 by BICR
Secondary	
To evaluate the PFS of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• PFS per RECIST v1.1 by BICR
To evaluate ORR and PFS of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC, in subgroups defined by PD-L1 expression, LAG-3 expression, FG-L1 expression	• ORR and PFS per RECIST v1.1 by BICR
To evaluate the duration of response (DoR) of nivolumab plus relatlimab in combination with PDCT relative to	• DoR per RECIST v1.1 by BICR, including DoR at 6, 12 and 18 months

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	
To evaluate the safety and tolerability of nivolumab plus relatlimab in combination with PDCT in histologically confirmed 1L Stage IV or recurrent NSCLC	• Incidence of AEs, SAEs, TRAEs, IMAEs and select AEs
Exploratory	
To evaluate OS of nivolumab plus relatlimab in combination with PDCT vs nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• OS
[redacted]	
To characterize the immunogenic potential of relatlimab and nivolumab in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• Anti-relatlimab and anti-nivolumab antibodies and their relationship with other outcome measures
To characterize PK of relatlimab and nivolumab in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• PK measurements of relatlimab and nivolumab
To characterize changes in disease-related symptoms, and physical function in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• Mean change from baseline [redacted]
To characterize participant perceptions of the bothersomeness of the side effects of treatment in participants with histologically confirmed 1L Stage IV or recurrent NSCLC	• Proportion of participants experiencing bother [redacted]

Abbreviations: 1L = first line; AE = adverse event; BICR = blinded independent central review; [redacted] LAG-3 = lymphocyte-activation gene 3; NSCLC = non-small cell lung cancer; [redacted] ORR = overall response rate; OS = overall survival; [redacted] PDCT = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PGIC = Participant Global Impression of Change; PGIS = Participant Global Impression of Severity; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TRAE = treatment related adverse event.

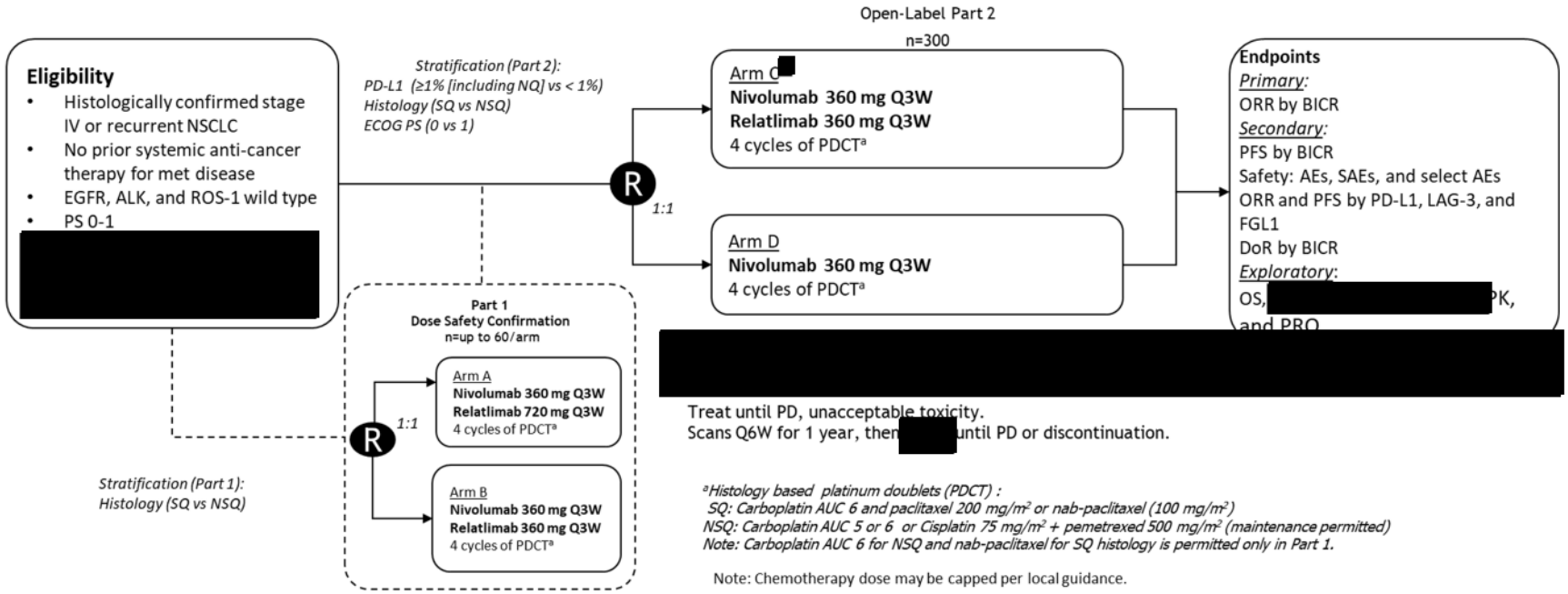
5 STUDY DESIGN

5.1 Overall Design

This multi-center, randomized trial will evaluate the efficacy and safety of the combination of nivolumab plus relatlimab and PDCT vs nivolumab and PDCT in adults with untreated Stage IV or recurrent NSCLC. The study will be carried out in 2 parts: Part 1, a site-and-subject blind dose safety confirmation and Part 2, an open-label, randomized, controlled trial.

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

Figure 5.1-1: Study Design Schematic



Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; AUC = area under the concentration-time curve; BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group Performance Score; EGFR = epidermal growth factor; [redacted] NSCLC = non-small cell lung cancer; NQ = non-quantifiable; NSQ = non-squamous; ORR = overall response rate; OS = overall survival; PD = progressive disease; PDCT = platinum doublet chemotherapy; [redacted] PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PRO = patient-reported outcome; Q3W = every 3 weeks; SAE = serious adverse event; SQ = squamous.

Part 1 - Dose safety confirmation (n ≈ up to 120): Site-and-subject blinded, randomized dose safety confirmation. Eligible participants will be randomized 1:1 to Arms A or B to evaluate the safety and tolerability of the combination of nivolumab plus relatlimab 720 mg and PDCT and confirm the safety profile. The relatlimab 360 mg Q3W dose in Arm B will be evaluated to generate additional safety data at this dose level. The randomization will be stratified by histology (SQ vs NSQ). After all treated participants have been followed up for a minimum of 12 weeks, the primary analysis will take place to determine whether the final established threshold for the dose-safety evaluable population has been met and to evaluate the totality of the Part 1 safety data.

In addition, the proportion of TRAEs leading to discontinuation within 12 weeks of the first dose will be monitored for each arm [redacted]

If, based on the dose safety confirmation, the regimen including relatlimab 720 mg (Arm A) is confirmed to be safe, then this dose level will be evaluated in Part 2 of the trial against the control arm. If, based on the dose safety confirmation, the regimen including relatlimab 720 mg is not confirmed to be safe, but the regimen including relatlimab 360 mg (Arm B) is confirmed to be safe, then the latter will be the dose evaluated in Part 2. If both Arm A and Arm B are confirmed to be safe, or Arm A is confirmed to be safe while Arm B is not, then the selected dose for development contained in Arm A (relatlimab 720mg Q3W) will be the one used in Part 2. If neither regimen is confirmed to be safe at any point during the dose safety confirmation, then Part 2 of the study would not take place. Relatlimab dose of 360 mg Q3W was selected from the conduct of Part 1, target receptor engagement, and benefit-risk assessment considerations at asset level.

In addition, for Part 1, an external control arm will be constructed. This approach will be described in detail in a statistical analysis plan (SAP).

Part 2 (n = 300): Randomized, open-label, controlled trial that will further evaluate the efficacy and safety of the nivolumab, relatlimab plus chemotherapy combination vs nivolumab plus chemotherapy. [redacted] At this time, participants that are in screening and found to be eligible will be randomized 1:1 into experimental Arm C or control Arm D of Part 2 of the trial. [redacted] The stratification factors for randomization in Part 2 are histology (SQ vs NSQ), ECOG performance status (0 vs 1) and PD-L1 level (≥ 1% [including NQ] vs < 1%).

5.1.1 Screening Phase

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participant's standard care. After signing the informed consent form (ICF), participants will be evaluated for entry criteria during the Screening Period [redacted] before randomization. Re-enrollment after screen failure will be allowed. Imaging of the brain with magnetic resonance imaging (MRI) (with and without contrast) is required of all participants during Screening. Computed tomography (CT) of the brain (without and with contrast) can be performed if MRI is contraindicated. A 12-lead electrocardiogram (ECG) and echocardiogram are required during screening.

[redacted]

5.1.2 On-treatment Phase

The Part 1 dose safety confirmation period is 12 weeks after the first dose. Up to approximately 120 eligible participants to enroll in the study will be randomized 1:1 to experimental Arms A or B. Nivolumab plus relatlimab, the immune checkpoint inhibitors hereon referred to as immunotherapy, will be administered in a site-and-subject blinded manner, whereas chemotherapy will be administered as open label.

Arm A: Nivolumab 360 mg Q3W + relatlimab 720 mg Q3W + 4 cycles of histology-based PDCT

Arm B: Nivolumab 360 mg Q3W + relatlimab 360 mg Q3W + 4 cycles of histology-based PDCT

During the treatment phase of Part 2 of the study, participants will receive the following treatments. Immunotherapy and chemotherapy will be administered as open-label interventions.

Arm C: Nivolumab 360 mg Q3W + relatlimab 360 mg[a] Q3W + 4 cycles of histology-based PDCT[b] or

Arm D: Nivolumab 360 mg Q3W + 4 cycles of histology-based PDCT[b]

[a] The relatlimab dose to be included in Arm C will be determined by the outcome of the dose safety confirmation that will take place in Part 1 of the study and other benefit-risk considerations at asset level. This was determined to be relatlimab 360 mg Q3W.

[b] Histology-based PDCT will be as follows:

NSQ: Carboplatin area under the concentration-time curve (AUC) 5 or 6* or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 (maintenance permitted)

SQ: Carboplatin AUC 6 + paclitaxel 200 mg/m^2 or nab-paclitaxel 100 mg/m2

***NOTE:** Carboplatin AUC 6 for NSQ and nab-paclitaxel for SQ histology is permitted only in Part 1.

Dose reductions are not permitted for immunotherapy.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval (refer to Table 2-2). Participants will be closely monitored for AEs throughout the study. Samples will be collected before and after study drug administration for PK analysis and pharmacodynamic parameter measurements. See Section 2 for further details.

All participants will be treated until progression, presence of intolerable toxicities, withdrawal of consent, or study end, whichever comes first. Continuous safety evaluations and tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Participants will be allowed to continue study treatment until the first occurrence of any of the following situations:

- Progressive disease (PD) defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5) unless participants meet criteria for treatment beyond progression (Section 8.1.3).
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to study therapy.
- Participant meets criteria for discontinuation of study treatment as shown in Section 8.1.

5.1.3 Follow-up Period

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. The duration of the study from start of randomization in the dose safety confirmation

period to the final analysis of PFS is approximately 48 months [redacted]

Timing for long-term follow-up will be as follows: Assessments should continue as described in Table 2-3.

- Safety Follow-up: [redacted] If the participant discontinues study drug due to a clinically significant AE, the participant will be followed until resolution of the AE or the event is considered to be stable and/or chronic.
- Tumor Assessment and Response Follow-up: Participants who discontinue study treatments for reasons other than PD as per BICR or death should continue to have tumor assessment as per Section 9.1.1.1 until PD as per, death, lost to follow-up, or withdrawal of consent, whichever happens earlier. Participants with a history of brain metastasis or symptoms should continue to have surveillance MRIs (without and with contrast) per standard of care [redacted] or sooner if clinically indicated.
- Survival Follow-up: [redacted] For participants who are discontinued without BICR-confirmed PD, tumor assessments should continue to be performed based on Table 2-3. Information on the subsequent PD, subsequent anti-cancer therapy, and outcome must be collected.

5.1.4 Data Monitoring Committee and Other External Committees

An independent DMC will be utilized to provide general oversight and safety considerations for Study CA224104 during Part 2 phase. The independent DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The independent DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for nivolumab/relatlimab. The independent DMC will act in an advisory capacity to BMS and will monitor participant safety data for Part 2 of the study.

BMS will have responsibility for the overall conduct of the study, including managing the communication of study data. BMS will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Details of the independent DMC responsibilities and procedures will be specified in the DMC charter.

In addition to the DMC, a safety committee (SC) consisting of BMS research and development representatives (including clinical development, drug safety, and statistics) and external representatives (including a selection of the study investigators) will regularly meet to evaluate the accumulating safety data of participants on the dose safety confirmation portion of the study (Part 1) and provide input to interpret safety signals. Information reviewed at each time point may include disposition, demographics, AEs, SAEs, TRAEs, TRAEs leading to discontinuation, exposure, death data, and any other data deemed relevant (laboratory, pathology, autopsy reports, physical descriptions). The minutes of these meetings will be documented in the Trial Masterfile. The SC will not share responsibilities with the DMC (ie, the SC is responsible for monitoring Part 1 and the DMC for Part 2). Decisions on safety, toxicity, and benefit-risk regarding each dose level will be solely the responsibility of BMS and will take account of the totality of the data available. [redacted]

Although the SC will meet only during Part 1 of the study, the safety of the selected dose will continue to be monitored in Part 2. The DMC will regularly review any potential emergent safety signal that was not observed in Part 1 (note that the DMC will receive the most recent Part 1 safety data as well).

5.1.5 Blinded Independent Radiology Central Review

A BICR is recommended by regulatory agencies in situations where clinical site image interpretation is variable and results of image measurements are important for eligibility determination, safety, and/or efficacy endpoints. Specifically, BICR of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of ORR and PFS. Sites should submit all images to BICR on a continuing basis. However, should the BICR interpretation be in conflict with the local evaluation, treatment decisions will be based on investigator assessment and not the BICR results provided to the site. See Section 9.1.1.3 for more information on BICR confirmation of progression.

5.2 Number of Participants

In the dose safety confirmation (Part 1), up to approximately 120 participants will be randomized 1:1 to treatment Arms A or B (ie, 60 participants per arm).

In Part 2, approximately 300 participants will be randomized 1:1 to the experimental arm, C, or the control arm, D (ie, 150 participants per arm).

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. [redacted] or the final date on which data is to be collected for survival follow-up, whichever occurs later. [redacted]

5.4 Scientific Rationale for Study Design

Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor-infiltrating T-cells (eg, PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (eg, increased Tregs). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of Tregs.

Despite recent innovations in cancer treatment, alternative therapies are needed for participants with advanced NSCLC (see Section 3.2). The recent Food and Drug Administration (FDA) approvals of nivolumab in combination with ipilimumab and nivolumab in combination with ipilimumab plus PDCT in 1L NSCLC increase the armamentarium of immunotherapy combinations that have improved the prognosis of this population. However, still less than 50% of participants are expected to benefit from anti–PD-1/PD-L1 combination therapy, highlighting the need for further investigation into other strategies such as simultaneous inhibition. Combination immune-modulating therapies have an emerging role in producing deep and durable responses in a variety of tumor types. Early clinical data from trials studying relatlimab in combination with nivolumab, and the combination of nivolumab with chemotherapy, suggest that there may be a potential for increasing benefit by combining these drugs due to the vast amount of receptors that are targeted by their non-overlapping mechanisms of action (see Section 3.2.3). Overall, the safety profile of relatlimab in combination with nivolumab has been manageable, and there were no known additional toxicities with the relatlimab combination with nivolumab. Similarly, the safety profile of nivolumab has been manageable both in combination with ipilimumab and in combination with chemotherapy. Therefore, it is expected that the addition of relatlimab to nivolumab and chemotherapy will provide an acceptable benefit-risk ratio.

5.4.1 Rationale for Exclusion of Participants with Known Epidermal Growth Factor, Anaplastic Lymphoma Kinase, ROS-1, and B-rapidly Accelerated Fibrosarcoma Proto-oncogene V600E Alterations

Epidermal growth factor receptor (EGFR)-mutant tumors commonly display lower TILs, PD-L1 expression, and tumor mutational burden than EGFR-wild-type tumors. Consistent with this, participants with EGFR-mutated carcinomas derive less clinical benefit from PD-1 axis blockade. In addition, clinical trials have demonstrated that participants with actionable molecular alterations such as EGFR mutations or ALK translocations have lower response rates to checkpoint inhibition with PD-1 or PD-L1 inhibitors. Treatments for EGFR mutations, anaplastic lymphoma kinase (ALK) translocations, ROS-1 rearrangements, and B-rapidly accelerated fibrosarcoma proto-oncogene (BRAF)V600E mutations have shown impressive results and are now FDA approved in

NSCLC. For that reason, 1L standard of care for participants with any of these clinically actionable alterations is targeted therapy rather than immunotherapy and/or chemotherapy. Participants known to have these abnormalities will be excluded from this study. Excluding these participants will help to reduce the potentially confounding effects of these abnormalities on the study endpoints.

Since BRAFV600E is not yet widely tested, it will not be a requirement to test for BRAF mutations at screening in this study. However, participants with a known BRAFV600E mutation will be excluded.

5.4.2 Rationale for Dose Safety Confirmation

[redacted]

In order to confirm the safety profile of relatlimab in combination with nivolumab at the chosen development dose, a dose safety confirmation phase will be conducted prior to Part 2 of the study. The relatlimab 360 mg Q3W dose will be evaluated to generate additional safety data at this dose level. [redacted] participants will be treated with each regimen and will be followed for at least 12 weeks after the first dose to identify the rate of participants that experience treatment-related toxicities that lead to discontinuation during the 12-week evaluation period. Continuous monitoring of participant safety will be performed to review cumulative toxicity data.

[redacted]

[redacted]

5.4.3 Rationale for Shortened Infusion Time for Nivolumab plus Relatlimab

Long infusion times, especially when multiple agents are administered to an individual, place a burden on participants and treatment centers. Establishing that nivolumab and relatlimab can be safely administered using a shorter infusion time of 30 minutes duration will diminish this burden, provided the safety profile remains manageable.

Previous clinical studies of nivolumab in combination with relatlimab have used a 60-minute infusion duration. However, relatlimab doses [redacted] have been safely administered as a single agent vial (SAV) over 60 minutes in study CA224020. In this study, the higher dose of 720 mg of relatlimab to be co-administered with nivolumab over 30 minutes will not exceed this IV administration rate. Additionally, nivolumab and relatlimab have been previously co-administered as a FDC with no apparent increase in infusion-related reactions, compared with sequential administration.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or relatlimab clinical studies or the combination of nivolumab and relatlimab. Furthermore, a 30-minute break after the immunotherapy infusion will ensure the appropriate safety monitoring before the start of the chemotherapy infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab in combination with relatlimab.

[redacted]

5.4.4 Rationale for Choice of Chemotherapy

1L treatment of advanced NSCLC is histology specific. In SQ NSCLC, carboplatin plus paclitaxel is a standard of care regimen for participants with newly diagnosed advanced or metastatic NSCLC who do not have EGFR mutations or ALK translocations. Participants with NSQ histology may receive cisplatin or carboplatin with pemetrexed with optional pemetrexed as maintenance therapy. Although some but not all meta-analyses and randomized studies have demonstrated that cisplatin-based regimens may produce improved survival compared to carboplatin-based regimens, many participants are not ideal candidates for cisplatin due to its higher toxicity. Carboplatin-based chemotherapy is routinely used in clinical practice and clinical trials.

Prior data from CA209012 suggest similar efficacy and safety when combining nivolumab with chemotherapy, regardless of the chemotherapy backbone. Participants with SQ and NSQ histology may receive the following platinum-doublet backbone in their regimens:

- SQ histology: 4 cycles of carboplatin AUC 6 + paclitaxel 200 mg/m^2 or carboplatin AUC 6 + nab-paclitaxel (100 mg/m^2)[a]
- NSQ histology: 4 cycles of carboplatin AUC 5 or 6[a] + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

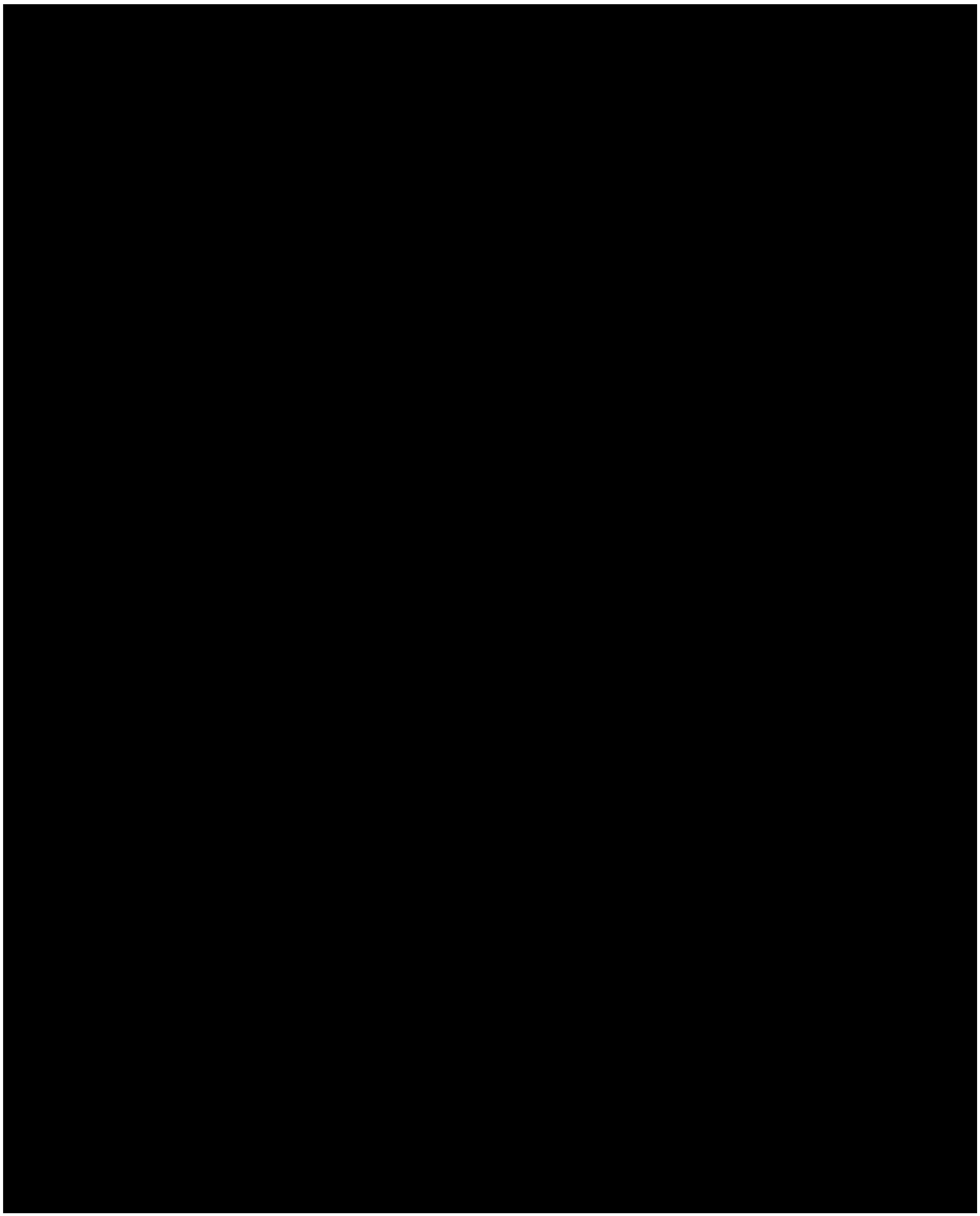
[a] Nab-paclitaxel for SQ and carboplatin AUC 6 for NSQ histology is applicable to Part 1 only.

[redacted] and carboplatin dose has been restricted to AUC 5 for non-squamous histology to align with global standard of care and to reduce variation in management of this participant population.[1]

5.4.5 Rationale for Choice of Control Arm

A key requirement stemming from current health authority guidelines for evaluation of treatment combinations is to demonstrate the contribution of each component to the overall effect of the regimen being tested. A typical way to achieve this is by comparing the combination therapy to the one or more of the monotherapies to prove non-inferiority or superiority. Nivolumab plus chemotherapy was tested in study CA209227. Even though the combination did not achieve significance on its primary endpoint of prolonging OS vs PDCT alone in NSQ participants, the nivolumab plus chemotherapy regimen was demonstrated to be active and tolerable in the all comer population across histologies and regardless of PD-L1 expression. Specifically, the 12-month OS rates were 67% and 59% with nivolumab plus PDCT and PDCT alone, respectively. In all randomized participants and in SQ NSCLC, nivolumab plus PDCT showed improved efficacy vs PDCT across endpoints. In descriptive analyses, PFS, ORR, and DoR were numerically improved with nivolumab plus chemotherapy vs chemotherapy by itself. ORR for the combination in the NSQ participants was 48.1% vs 25.7% for PDCT. In the SQ participants, ORR was 59.8% vs 32.4% in the chemotherapy arm. For comparison with historical data, ORR for the Phase 3 studies that led to the regulatory approval of the pembrolizumab plus chemotherapy combination was 47.6% in NSQ participants and 57.9% in the SQ population. Likewise, in NSQ subjects, median PFS (mPFS) was 8.7 months for nivolumab plus PDCT vs 5.8 months in the PDCT only group (HR = 0.67); whereas in the SQ participants mPFS was 7.1 months for nivolumab plus PDCT vs 4.4 months in the PDCT arm (HR = 0.51). The mPFS of pembrolizumab plus PDCT in the aforementioned trials was 8.8 months in NSQ participants (HR = 0.52) and 6.4 months in the SQ population (HR = 0.56).

[redacted]



[redacted]

5.4.8 Rationale for ORR as a Primary Endpoint in Part 2

ORR is an acceptable Phase 2 endpoint in oncology studies in NSCLC that allows results to be assessed earlier when compared with survival-based endpoints. Early access to ORR data is necessary due to the rapidly changing landscape in NSCLC and is considered sufficient to establish proof-of-concept to help guide further development of the investigational agent(s). An advantage of ORR over survival-based endpoints is the direct attribution of tumor response to therapy because in the absence of treatment, spontaneous tumor regression is highly unlikely. Furthermore, ORR has been demonstrated to be a potential surrogate endpoint for checkpoint inhibitor therapies in NSCLC. A meta-analysis of 14 trials including over 10,000 participants with advanced NSCLC submitted to the FDA between 2003 and 2013 demonstrated a strong trial-level association between ORR and PFS.[42,43,44]. In the CA224-047 trial of nivolumab + relatlimab FDC vs nivolumab monotherapy in first line advanced melanoma, the clinically meaningful improvement of ORR (43.1% vs 32.6%) led to a statistically significant improvement in PFS [10.1 months (95% CI, 6.4–15.7) vs 4.6 months (95% CI, 3.4–5.6)].[45,46]

In a meta-analysis conducted using pooled data from 63 trials and 78 immune checkpoint therapy treatment arms (n > 30,000), representing 15 different tumor types across different lines of therapies, including NSCLC, ORR, and 6-month DoR was shown to be prognostic for 12-month OS.[47] The primary ORR assessment will be performed by BICR in Part 2 and will be further characterized by the durability and depth of responses to establish the contribution of components of relatlimab and nivolumab.

5.4.9 Rationale for Stratification

In order to minimize the potential for imbalances across treatment arms, there will be 3 stratification factors utilized in Part 2 of this trial: histology (SQ vs NSQ), PD-L1 expression (≥ 1% tumor cell surface expression [includes NQ] versus < 1% tumor cell surface expression) and ECOG performance status (0 vs 1).

The prognostic implications of histology are well established, even before the advent of immunotherapy,[48] hence different chemotherapy regimens are indicated according to histology, with pemetrexed maintenance currently favored only for adenocarcinoma.

With regard to PD-L1 expression, previous clinical studies with nivolumab monotherapy have shown participants with PD-L1 positive tumors may have better outcomes with PD-1-based therapies than those with non-expression. Participants in the current trial will therefore be stratified by PD-L1 status as the effect of PD-L1 expression on response to anti-PD-1 and anti-LAG-3 combination therapies is not yet known. The proportion of NQ for PD-L1 expression is currently estimated at 5%-10% in 1L NSCLC trials. Given the small proportion of participants with NQ sample, NQ will be categorized with the PD-L1 ≥1% group. The PD-L1 ≥ 1% group was chosen because the prevalence of this group within the quantifiable participants is expected to be slightly

higher (57%-60%) than of the PD-L1 < 1% group, and thus the presence of NQ participants in the PD-L1 ≥ 1% group is less likely to dilute treatment effect in this group; in addition, it will be slightly more robust against a potential imbalance of NQ participants across arms.[49,50]

ECOG PS is also a well-established prognostic clinical factor in NSCLC.[49,50,51]

Although ECOG performance status (PS) and gender are both well-established prognostic clinical factors in NSCLC,[52] ECOG (0 vs 1) was selected as a stratification factor in this study on the basis of the higher prognostic value compared with gender. In the nivolumab plus PDCT arm in Part 2 of the CA209227 1L NSCLC study, median OS was 24.3 months in subjects with ECOG PS of 0 vs 17.9 months in participants with ECOG PS of 1. For gender, the median OS was 17.9 months in males vs 20.7 months in females.[43, 52]

Due to its smaller sample size and because its primary purpose is safety, Part 1 will be stratified by histology (SQ vs NSQ) only.

5.4.10 Rationale for Biomarker Assessment

Immune checkpoint signaling [redacted] significantly dampens anti-tumor immune responses in different tumor types, including NSCLC. Unfortunately, not all participants respond to immune checkpoint blockade; therefore, there is a compelling need for a better understanding of factors (eg, biomarkers) that would predict response and progression.

[redacted]

5.4.11 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some participants treated with immune system-stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical OR and/or stable disease (SD). This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has been observed with ipilimumab monotherapy as well, suggesting that it is not a drug-specific occurrence. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible, small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, participants will be allowed to continue

immunotherapy after initial investigator-assessed RECIST v1.1-defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Such participants must discontinue study therapy upon evidence of further progression as defined in Section 8.1.3.

5.4.12 Rationale for Patient Reported Outcomes Assessments

The evaluation of the participant's experience in the evaluation of biopharmaceutical treatments is important to fully understand the impact of such products on how participants feel and function. Patient-reported outcomes (PROs) have been incorporated in oncology trials in order to more fully understand the participant's experience. In addition, there is an increased focus from the clinical community on the specific concepts that are influenced by therapeutic products, including disease-related symptoms, symptomatic AEs, and physical functioning. When used in tandem with traditional clinical measures, the [redacted] can provide additional context for safety and efficacy results. In the current trial, the participant's experience will be directly measured through the [redacted] the [redacted] from the [redacted] the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC). The Center for Drug Evaluation and Research has determined that the [redacted] demonstrated adequate evidence of content validity and cross-sectional measurement properties (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of NSCLC in the context of the participant population being studied in this trial.

5.5 Justification for Immunotherapy Dose

Two relatlimab doses, 360 mg Q3W and 720 mg Q3W, were selected to be evaluated in co-administration with 360 mg nivolumab Q3W plus platinum-based chemotherapy in the dose safety confirmation portion of this study (Part 1). [redacted] In addition, both immunotherapy drugs will be co-administered in a single IV bag. The PK and safety profile of relatlimab in co-administration with nivolumab is not expected to be different than that of sequential administration implemented previously in other clinical trials. Please also refer to the details on clinical activity and benefit-risk assessment of relatlimab and nivolumab co-administration in Sections 3.2.4 and [redacted] respectively.

5.5.1 Justification for Nivolumab Dose

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, SCCHN, colorectal cancer, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body weight-based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[53,54]

Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W [redacted] dosing regimens can reduce the burden to participants of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

[redacted]

5.5.2 Justification for Relatlimab Doses

[redacted]

[redacted] The PK and safety profile of relatlimab when co-administered with nivolumab is not expected to be different than that of sequential administration implemented previously in other clinical trials. Please also refer to the details on the benefit-risk assessment of relatlimab and nivolumab co-administration in [redacted]

[redacted]

5.6 Clinical Pharmacology

Clinical pharmacology of relatlimab in combination with nivolumab is currently being evaluated in a number of tumor types, including melanoma, NSCLC, gastric cancer, and HCC. The individual relatlimab and nivolumab PK is not altered when the 2 drugs are given in combination. The effect of other drugs on the PK of relatlimab has not been formally investigated. However, it is unlikely that other chemotherapies will have an impact on the PK of relatlimab given that relatlimab is an IgG4 monoclonal antibody, which is likely eliminated by mechanisms similar to that of other antibodies, namely nonspecific catabolism.

5.6.1 Nivolumab Clinical Pharmacology Summary

Nivolumab pharmacokinetics (PK) was assessed using a popPK approach for single-agent nivolumab.

The PK of single-agent nivolumab was studied in participants over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%), resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in participants with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in participants with completely resected melanoma, as the geometric mean population clearance is 24% lower in this participant population compared with participants with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The popPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline lactate dehydrogenase (LDH), PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a popPK analysis in participants with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between participants with renal impairment and participants with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by popPK analyses in participants with HCC and in participants with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN]

and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any aspartate aminotransferase [AST]) and in HCC participants with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between participants with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator's Brochure and product label.

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and

institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) PS of ≤ 1 at screening and confirmed prior to randomization.

b) Participants must have a life expectancy of at least 3 months at the time of first dose.

c) Histologically confirmed metastatic NSCLC of SQ or NSQ histology with Stage IV A/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease.

[redacted]

e) No prior systemic anti-cancer treatment (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

f) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to enrollment.

g) Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.

h) Prior palliative radiotherapy to non-central nervous system (CNS) lesions must have been completed at least 2 weeks prior to treatment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first treatment are strongly encouraged to receive palliative radiotherapy prior to treatment.

i) Measurable disease by CT or MRI per RECIST v1.1 criteria (Appendix 5); radiographic tumor assessment performed [redacted] prior to randomization.

j) Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site after the completion of radiation therapy.

3) Age and Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants

i) Females, ages 18 or local age of majority.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Assessments.

vi) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

viii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4)

ix) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP.

OR

[redacted]

b) Male Participants

i) Males, ages 18 or local age of majority.

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant.

iv) Male participants are required to use a condom during the intervention period and for at least 6 months after the last chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.

v) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 6 months after the last chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) dose of the male participant's study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.

vi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the intervention period and for at least 6 months after the last chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin), whichever is longer.

vii) Male participants must refrain from donating sperm during the intervention period and for at least 6 months after the last chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) dose (or a total of 11 months for male participants receiving cisplatin), whichever is longer.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are breastfeeding

b) Mutation status:

i) EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All participants with NSQ histology must have been tested for EGFR mutation status; use of an FDA-approved or local Health Authority test (tissue or blood) is strongly encouraged. Participants with NSQ histology and unknown EGFR status are excluded.

ii) ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with NSQ histology must have been tested for ALK mutation status; use of an FDA-approved or local Health Authority test is strongly encouraged. Participants with NSQ histology and unknown ALK status are excluded.

iii) ROS-1 translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with NSQ histology must have been tested for ROS-1 translocation status. Participants with NSQ histology and unknown ROS-1 status are excluded.

iv) Known BRAFV600E mutations which are sensitive to available targeted inhibitor therapy are excluded. If BRAF mutation status is unknown or indeterminate, participant may enroll.

c) Participants with untreated CNS metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Brain imaging performed [redacted] prior to randomization must document radiographic stability of CNS lesions and should be performed after completion of any CNS-directed therapy.

d) Participants with leptomeningeal metastases (carcinomatous meningitis).

e) Concurrent malignancy requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early-stage basal/SQ cell skin cancer or noninvasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

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

g) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

h) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome-defining opportunistic infection within the last year, or a current CD4 count <350 cells/μL. Participants with HIV are eligible if:

i) they have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study.

i) they continue on ART as clinically indicated while enrolled on study.

ii) CD4 counts and viral load are monitored per standard of care by a local health care provider.

NOTE: Testing for HIV must be performed at sites where mandated locally (participants enrolled with known HIV need monitoring of CD4 counts and viral load during the study and ART administered as clinically indicated). HIV-positive participants must be excluded where mandated locally (see Appendix 8).

i) Participants with serious or uncontrolled medical disorders.

j) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

k) Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

[redacted]

m) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

n) ***Not Applicable as per Amendment 02:*** Severe acute respiratory coronavirus 2 (SARS-CoV-2) infection (either suspected or confirmed) within 12 weeks of screening.

o) Severe infection within 4 weeks prior to screening

i) Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical trial physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

Note: Coronavirus disease 2019 (COVID-19) PCR viral testing may be required prior to randomization based on specific country/regional guidelines, and the result of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.

2) Prior/Concomitant Therapy

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

b) Prior treatment with LAG-3-targeted agents.

c) Concurrent use of immunosuppressive agents.

d) Concurrent use of immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3).

e) Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

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

g) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

h) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

3) Physical and Laboratory Test Findings

a) Participants with ≥ Grade 2 peripheral neuropathy

b) [redacted]

i) > 2 × institutional upper limit of normal (ULN).

ii) Participants with [redacted] between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 × ULN. If [redacted] are between >1 to 2 × ULN within 24 hours, the participant may undergo a cardiac evaluation and be considered for treatment, based on a favorable benefit-risk assessment by the Investigator. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If [redacted] beyond 24 hours are < 2 × ULN, the participant may undergo a cardiac evaluation and be considered for treatment based on a favorable benefit-risk assessment by the Investigator. Notification of the decision to enroll the participant has to be made to the BMS Medical Monitor or designee.

c) Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to start of study treatment.

d) White blood cells < 2000/μL (SI units: < 2×10^9/L).

[redacted]

e) Absolute Neutrophil Count (ANC) < 1500/μL (SI units: < 1.5×10^9/L)

[redacted]

f) Platelets < 100,000/μL (SI units: < 100×10^9/L)

g) Hemoglobin < 9.0 g/dL (SI units: < 90 g/L)

h) Serum creatinine > 1.5 × ULN, unless creatinine clearance (CrCl) ≥ 50 mL/min (measured or calculated using the Cockcroft-Gault formula)

i) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT): > 3.0× ULN (> 5× ULN if liver metastases are present)

j) Total bilirubin (TB) > 1.5× ULN (except participants with Gilbert syndrome who must have a TB level of < 3.0× ULN)

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

4) Allergies and Adverse Drug Reaction

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

b) Any contraindication to any of the study drugs. Investigators should refer to local package insert or Summary of Product Characteristics.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

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

c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a participant's ability to comply with the study requirements, substantially increase risk to the participant, or impact the interpretability of study results.

d) Participants with a history of screen failure to any anti-PD-1 or anti-PD-L1 antibody clinical trial due to PD-L1-negative status.

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements, as

applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening or Dose Safety Confirmation Period

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

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

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

Testing for asymptomatic SARS-CoV-2 infection, for example by RT-PCR or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved and
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines.

7 TREATMENT

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

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

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

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

Table 7-1: Study Treatments for CA224104

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label[a]	Packaging / Appearance	Storage Conditions (per label)
Relatlimab[b]	[redacted]	IP	Open	[redacted]	Store 2 to 8°C; do not freeze; protected from light
Nivolumab[c]	10 mg/mL	IP	Open	100 mg/vial (10 mg/mL) 10 mL vial 4 or 5 vials per carton	Store 2 to 8°C; do not freeze; protected from light
Carboplatin	10 mg/mL	IP	Open	450 mg vial (10 mg/mL) 45 mL 4 vials/carton	Product should be stored as per market product conditions
Cisplatin	100 mg/vial (1 mg/mL)	IP	Open	100 mg/vial (1 mg/mL) 4 vials/carton	Product should be stored as per market product conditions
Paclitaxel	6 mg/mL	IP	Open	100 mg/vial (6 mg/mL) 16.7 mL 4 vials/carton	Product should be stored as per market product conditions
Nab-Paclitaxel[d]	100 mg/vial	IP	Open	100 mg per vial and 1 vial per carton	Product should be stored as per market product conditions
Pemetrexed	500 mg/vial	IP	Open	500 mg per vial and 1 vial per carton	Product should be stored as per market product conditions

Abbreviations: IP = Investigational Product; Non-IMP = Non-Investigational Medical Product; SmPc = summary of product characteristics.

[a] The immunotherapy drug vials will be delivered to the pharmacy as open label, whereas the site personnel will receive the final infusion bag in a blinded manner in Part 1. Part 2 is open-label.

[b] May be labeled as either "BMS-986016-01" or "Relatlimab".

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

[d] For BMS provisioned nab-paclitaxel the product may be labeled as "paclitaxel nab" or "Abraxane".

Non-BMS products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. In these cases, products may be in a different pack size/potency/pharmaceutical form than listed in the table. These products should be prepared/stored/administered in accordance with the package inserts or SmPC.

7.1 Treatments Administered

During the treatment phase, participants will receive one of the treatment regimens by arm described in Table 7.1-1. Immunotherapy will be administered in a blinded manner, while chemotherapy will be unblinded in Part 1. Part 2 will be open-label. Dose reductions are not permitted for immunotherapy study treatments.

Table 7.1-1: Selection and Timing of Dose for Each Participant

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Arm A	Nivolumab 360 mg Relatlimab 720 mg Histology-based PDCT	Q3W	IV infusion
Arm B	Nivolumab 360 mg Relatlimab 360 mg Histology-based PDCT	Q3W	IV infusion
Arm C	Nivolumab 360 mg Relatlimab 360 mg[a] Histology-based PDCT	Q3W	IV infusion
Arm D	Nivolumab 360 mg Histology-based PDCT	Q3W	IV infusion

Abbreviations: IV= intravenous; PDCT = platinum doublet chemotherapy; Q3W = every 3 weeks.

[a] Or relatlimab 360 mg Q3W depending on the dose safety confirmation analysis.

7.1.1 Immunotherapy Dosing

Participants will receive masked nivolumab and relatlimab, followed by chemotherapy on Day 1 of every 3-week cycle. In Arms A, B, and C, nivolumab will be co-administered with relatlimab in a single bag IV over approximately 30 minutes. Arm D participants will receive nivolumab IV over approximately 30 minutes. [redacted] Participants should be carefully monitored for infusion reactions during co-administration. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.1. The 4 cycles of chemotherapy will be administered in all arms per Section 7.1.2. At the time of completion of the 4 cycles of chemotherapy, participants who have not experienced disease progression will continue to receive immunotherapy Q3W starting on Day 1 of the following cycle:

- There will be no dose escalations or reductions of immunotherapy allowed.
- Premedications are not recommended for the first dose of immunotherapy.
- Participants should be carefully monitored for infusion reactions during immunotherapy administration.
  - If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6.
- Participants should receive immunotherapy until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

- Doses of immunotherapy may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment according to Section 7.4.1.
- Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.
- The assessment for discontinuation of immunotherapy should be made separately from the assessment to discontinue chemotherapy.
- If criteria for discontinuation of immunotherapy are met, PDCT may continue until 4 cycles have been completed.
- If criteria for discontinuation of PDCT are met, immunotherapy may continue until progression or unacceptable toxicity, whichever occurs first.
- If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to all or any 1 study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

The immunotherapy injections can be infused undiluted or diluted. All infusions must be promptly followed by a diluent flush to clear the line of IP before starting the chemotherapy infusion(s).

The second infusion will always be the chemotherapy study drug(s) and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred. The time between immunotherapy and chemotherapy infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Instructions for dilution and infusion of immunotherapy injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

Study treatment will be dispensed by IRT at the study visits as listed in Section 2 (Schedule of Activities). Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

7.1.2 Chemotherapy Dosing

In all 4 study arms, 4 cycles of the histology-based PDCT option selected by the investigator will be administered on Day 1 Q3W. Participants with NSQ histology may also receive optional maintenance therapy with 500 mg/m^2 pemetrexed alone on Day 1 of each 3-week cycle until disease progression or unacceptable toxicity or other reasons specified in the protocol (Section 8.1.2).

Histology-based chemotherapy:

- SQ histology:
  - Carboplatin AUC 6 + paclitaxel 200 mg/m^2
  - Carboplatin AUC 6 + nab-paclitaxel 100 mg/m^2 [a]

- NSQ histology:
  - Carboplatin AUC 5 or 6[a] + pemetrexed 500 mg/m^2
  - Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

[a] Nab-paclitaxel for SQ and carboplatin AUC 6 for NSQ histology are applicable to Part 1 only.

All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

[redacted]

7.1.2.1 Paclitaxel and Carboplatin

Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC of 5 or 6 as a 30-minute IV infusion on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standards.

Paclitaxel dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Carboplatin should be given following paclitaxel on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = target AUC × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards.

Premedications for use with paclitaxel include the following:

- Oral or IV corticosteroid should be given according to local standard at a dose equivalent to dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or IV.
- IV diphenhydramine (or its equivalent) 50 mg and H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion.
- Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment.

7.1.2.2 Nab-Paclitaxel and Carboplatin (Part 1 Only)

Participants in Part 1 will receive nab-paclitaxel 100 mg/m^2 as a 30-minute IV infusion on Days 1, [redacted] cycle. Carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion should be administered immediately after nab-paclitaxel on Day 1 of each 3-week cycle or at doses per the local prescribing information. The infusion time can follow local institutional standards.

Nab-paclitaxel dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Carboplatin should be given following nab-paclitaxel on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = target AUC × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards. No premedication is required for nab-paclitaxel prior to administration.

7.1.2.3 Pemetrexed and Cisplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed include the following:

- Oral or IV corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg twice daily (BID) on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).
- Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator.

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m^2 infusion as per local standard practice on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Cisplatin will be administered to participants at least 30 minutes following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care, or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards of care.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. See Sections 7.4.2, 7.4.3, and 8.1 for more details.

All participants who will receive cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care.

Participants who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the PDCT (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such participants should follow the instructions in Section 7.1.2.4.

7.1.2.4 Pemetrexed and Carboplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed:

- Oral or IV corticosteroid premed for pemetrexed should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. IM injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1, followed by carboplatin at a dose of AUC 5 or 6 (Part 1) or AUC 5 (Part 2) as a 30-minute IV infusion on Day 1 of a 3-week treatment cycle, for up to 4 cycles.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% weight used to calculate the previous dose.

The carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula (see inclusion criterion in Section 6.1) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment. All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

7.1.2.5 Optional Continuation Maintenance

After Cycle 4 of chemotherapy, participants with NSQ histology who have SD or response are permitted to receive pemetrexed 500 mg/m^2 alone as maintenance therapy until disease progression or unacceptable toxicity.

7.2 Method of Treatment Assignment

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study via the IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. 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
- Date of birth

[redacted]

Once enrolled in IRT, enrolled participants that have met all eligibility criteria will be randomized through IRT. The following information is required for participant randomization:

- Participant number

[redacted]

Participants meeting all eligibility criteria will be stratified as follows:

- Part 1: By tumor histology (SQ vs NSQ). Participants will be randomized in a 1:1 ratio to Arms A and B. Enrollment will end after up to approximately 120 participants are randomized.
- Part 2: By tumor histology (SQ vs NSQ), ECOG performance status (0 vs 1), PD-L1 level (≥ 1 [includes NQ] vs < 1%). Participants will be randomized in a 1:1 ratio to treatment and control arms. Enrollment will end after approximately 300 participants are randomized.

The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

Part 1 is site-and-subject blinded to immunotherapy treatment only. Access to treatment codes will be restricted from all participants and site personnel prior to primary database lock, with exceptions as specified below. Chemotherapy treatment will be administered as open label.

Part 2 is open-label. [redacted]

[redacted]

[redacted]

7.4 Dosage Modification

No dose reductions or escalations for immunotherapy are permitted.

7.4.1 Dose Modification Criteria for Immunotherapy

All AEs/SAEs must be graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.

The criteria for dose delay, resumption, and discontinuation for immunotherapy have been integrated to apply to immunotherapy treatment with either nivolumab or nivolumab plus relatlimab, henceforth referred to as immunotherapy. Delay immunotherapy dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, warrants delaying the dose of study medication. Specific management guidelines (dose delay, resumption, and discontinuation) for expected AEs and SAEs for the nivolumab + relatlimab combination therapy can be found in Table 7.4.1-1. Additional information on management of AEs and SAEs with nivolumab and relatlimab is found in [redacted]

For participants who require delay of immunotherapy, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.2). Continue tumor assessments per protocol even if dosing is delayed.

The assessment for dose delays of immunotherapy should be made separately from the assessment to delay chemotherapy.

Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
[redacted]			
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3x and ≤ 5x upper limit of normal (ULN) or T.Bili > 1.5x and ≤ 3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T. bili > 3 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur and approval from Medical Monitor prior to resuming therapy
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management,

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
[redacted]			
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade $\leq$ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Lab abnormalities			
Other Drug-Related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia. Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Immunotherapy

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.6 on Treatment of Related Infusion Reactions

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; GBS = Guillain-Barre syndrome; MG = myasthenia gravis; SJS = Stevens-Johnson syndrome; T.bili = total bilirubin; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

7.4.2 Dose Delay Criteria for Chemotherapy

Chemotherapy drugs should be delayed for any of the events listed below. The delay should occur on treatment Day 1 [redacted]

- Absolute neutrophil count (ANC) < 1500/μL (SI units: < 1.5×10^9/L)
- Platelets < 100,000/μL (SI units: < 100×10^9/L)
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related AE (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or TB:
  - Grade 3 lymphopenia does not require dose delay.
  - If a participant has a baseline AST, ALT, or TB that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a participant has baseline AST, ALT, or TB within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

Dose modifications listed are specific to US Prescribing Information (USPI). Variations may apply per local label. Participants receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated CrCl decreases to < 50 mL/min (based on the Cockcroft-Gault formula). The other drug (pemetrexed) may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the rest of the cycles when the participant meets retreatment criteria. Note that pemetrexed can only be administered if CrCl is ≥ 45 mL/min (calculated per Cockcroft-Gault formula).

If a participant receiving carboplatin with paclitaxel must discontinue carboplatin, paclitaxel may be continued at the investigator's discretion.

If any non-hematologic AE meeting the dose delay criteria above is felt to be related to only 1 particular agent in the PDCT regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 7.4.3.2 to determine if dose reduction of the resumed agent is required.

If both drugs in the PDCT regimen are delayed, then the participant should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 7.4.4.2).

Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.

Dosing of immunotherapy *and* both chemotherapy agents should be delayed if any criteria for immunotherapy *or both* PDCT agents are met.

7.4.3 Dose Reductions

7.4.3.1 Dose Reduction for Immunotherapy

No dose reductions for immunotherapy are permitted.

7.4.3.2 Dose Reduction for Chemotherapy

Dose reductions for chemotherapy may be required and will be performed according to Table 7.4.3.2-1 or per institutional guidelines. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy. The dose reductions for each agent in the PDCT regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.3.2-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Carboplatin	Pemetrexed	Nab-Paclitaxel[a]	Paclitaxel	Cisplatin
Starting dose	AUC 6 or AUC 5	500 mg/m^2	100 mg/m^2	200 mg/m^2	75 mg/m^2
First dose reduction	AUC 5 (if starting dose is AUC 6) or AUC 4 (if starting dose is AUC of 5)	375 mg/m^2	75 mg/m^2	150 mg/m^2	56 mg/m^2
Second dose reduction	AUC 4 (if starting dose is AUC 6) or AUC 3 (if starting dose is AUC 5)	250 mg/m^2	50 mg/m^2	100 mg/m^2	38 mg/m^2
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

Abbreviation AUC = area under the concentration-time curve.
[a] Nab-paclitaxel for SQ histology is applicable to Part 1 only.

Dose modifications listed are specific to US prescribing information (USPI). Variations may apply per local label.

Any participants with 2 prior dose reductions for 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.3.3 Chemotherapy: Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE v5) are summarized in Table 7.4.3.3-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for PDCT are relative to that of the preceding administration. Generally, both chemotherapy agents in the PDCT regimen should be

dose reduced together for hematologic toxicity. [redacted] For incidences of chemotherapy induced anemia or cancer-associated anemia, red blood cell transfusions are recommended. In participants who refuse RBC transfusions, erythropoiesis-stimulating agents may be administered as per local standards.

Use local standards of care for other previously described supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Investigators are strongly recommended to have a high index of suspicion for infection and consider starting broad spectrum antibiotics early for any fever or signs of infection in participants with neutropenia. Please report any antibiotic or growth factor use on the electronic case report form (eCRF).

Dose modifications listed are specific to USPI. Variations may apply per local label.

Table 7.4.3.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

Toxicity	Carboplatin	Paclitaxel	Nab-Paclitaxel[a]	Pemetrexed	Cisplatin
Neutrophil Count Decreased					
Grade 4 ($< 500/mm^3$ or $< 0.5 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Platelet Count Decreased					
Grade 3 ($< 50,000$ - $25,000/mm^3$; < 50.0 - $25.0 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 ($< 25,000/mm^3$; $< 25.0 \times 10^9/L$)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level

[a] Nab-paclitaxel for SQ histology is applicable to Part 1 only.

7.4.3.4 Chemotherapy: Dose Reductions for Non-hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described in Section 7.4.3.2. All dose reductions should be made based on the worst-grade toxicity. Participants experiencing any of the toxicities during the previous cycle should have their chemotherapy delayed until retreatment criteria are met and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the PDCT regimen are not linked and may be reduced independently, as summarized in Table 7.4.3.4-1.

Table 7.4.3.4-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Carboplatin	Paclitaxel	Nab-Paclitaxel[b]	Pemetrexed	Cisplatin
Febrile neutropenia Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Diarrhea Grade ≥ 3	No change	Reduce 1 dose level	No change	Reduce 1 dose level	No change
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce 1 dose level	No change	No change	No change	Reduce 1 dose level
Neuropathy Grade 3-4	Discontinue	Discontinue	Reduce 1 dose level	Discontinue	Discontinue
CrCl < 50 mL/min	No change	Discontinue if CrCl < 20 mL/ min	No change	No change	Discontinue
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

Abbreviation: CrCl = Creatinine Clearance; USPI = US Prescribing Information.

[a] Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (≥ Grade 3) require(s) discontinuation. All other drugs may be continued.

Note: Dose modifications listed are specific to USPI. Variations may apply per local label.

[b] Nab-paclitaxel for SQ histology is applicable to Part 1 only.

7.4.4 Criteria to Resume Dosing

7.4.4.1 Criteria to Resume Treatment with Immunotherapy

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.1-1.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and** 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 8 weeks or more frequently if clinically indicated during such dosing delays.

7.4.4.2 Criteria to Resume Treatment with Chemotherapy

- Participants may resume treatment with chemotherapy when the ANC returns to ≥ 1500/µL (SI units: ≥ 1.5×10^9/L), the platelet count returns to ≥ 100,000/µL (SI units: ≥ 100×10^9/L), and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue).
- If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.
- When resuming chemotherapy treatment, please follow the dose-reduction recommendations in Section 7.4.3.2.
- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and** 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

7.4.5 Management Algorithms for Immuno-Oncology Agents

IO agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and relatlimab are considered IO agents in this protocol. Because of the potential for clinically meaningful TRAEs requiring early recognition and prompt intervention, management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

[redacted]

The above algorithms are found in the nivolumab and relatlimab IBs as well as in [redacted] of this protocol.

7.4.6 Treatment of Immunotherapy Infusion Reactions

Since nivolumab and relatlimab contain only human Ig protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE v5 guidelines.

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

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

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

For Grade 2 symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-

inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further immunotherapy will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before immunotherapy infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

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

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

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If

concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

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

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

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

At the time of receipt of the IP by the investigator or designee, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by BMS or sourced by the site. Package labeling should clearly identify the contents as retention samples and state that the IP should be stored in the restricted area with limited access.

Additional details regarding the retention process will be provided in the Pharmacy Manual (or in other written information) provided to the site.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. This will be source data verified by the BMS Unblinded Site Monitor through regularly scheduled monitoring visits.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any live/attenuated vaccine (eg, varicella; zoster; yellow fever; rotavirus; oral polio; and measles, mumps, rubella) within 30 days prior to randomization, during treatment, and until [redacted] post-last dose.
- Administration of a live or replication competent COVID-19 vaccine is prohibited within 30 days prior to randomization. Live or replication competent COVID-19 vaccines should not be used during the study, including the treatment period, safety follow up-period and within [redacted]

[redacted] following last dose of IP. COVID-19 vaccines that are NOT live nor replication competent are permitted during the study and after the last dose of IP.

- Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving relatlimab and/or nivolumab plus PDCT is unknown.

No data are available on the response to COVID-19 vaccines. The following are NOT live vaccines: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines (eg, influenza and pneumococcal vaccines), toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines), and replication-incompetent recombinant vector vaccines (eg, AstraZeneca/University of Oxford COVID-19 vaccine). Please contact the clinical trial physician or Medical Monitor with any questions related to COVID-19 vaccines.

- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

The investigator must also adhere to the contraindications, precautions, and drug interactions found in the USPI or local label for each of the chemotherapy agents.

7.7.2 Other Restrictions and Precautions

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

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

- Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Regular concomitant use of biphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in participants with bone metastases is allowed if initiated prior to first dose of study treatment.
- Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment.

7.7.3.1 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study treatment for participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study treatment in participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the BMS Medical Monitor.

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 8.1.2) in order to resume immunotherapy after palliative local therapy. If radiographic progression per RECIST v1.1 is identified prior to the initiation of palliative local therapy, sites must request a BICR from the third-party radiology vendor (Section 5.1.5). However, the initiation of palliative local therapy need not be delayed to await the assessment by the BICR.

The potential for overlapping toxicities with radiotherapy and immunotherapy currently is not known; however, anecdotal data suggest that it is tolerable. As concurrent radiotherapy and the immunotherapy regimens evaluated in this study have not been formally evaluated, whenever palliative radiotherapy is required for a tumor lesion, then immunotherapy should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming immunotherapy.

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab or relatlimab is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

All participants who discontinue study drug should comply with protocol-specified follow-up procedures as outlined in Table 2-3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness; see Section 8.2). If study drug is discontinued prior to the participant's completion of the study, the reason for discontinuation must be documented in the participant's medical records and entered on the appropriate eCRF page.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’ in the source data and in the eCRF. Tumor assessments for participants who discontinue study treatment without radiographic progression, confirmed by BICR (Section 5.1.5), should continue as per protocol (refer to Section 2) until radiographic progression is determined by BICR.

Chemotherapy dose reduction is allowed on study. Any participant with 2 prior dose reductions to 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Participants MUST discontinue IP for any of the following reasons:

- Participant’s request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. (The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. See Section 8.2.)
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under

specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

- Disease progression in the absence of clinical benefit as determined by the investigator.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the investigator and Sponsor.
- In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. The study treatment must be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

8.1.1 Immunotherapy Dose Discontinuation

Immunotherapy treatment should be permanently discontinued per criteria in Table 7.4.1-1 on Section 7.4.1.

- Discontinue immunotherapy for any AE, laboratory abnormality, or intercurrent illness which in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab and relatlimab dosing. For discontinuations due to neutropenia/neutrophil count decreased assessed to be related to study drugs by the Investigator, a discussion should take place with the BMS Medical Monitor (or designee) prior to discontinuation.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:
- Dosing delays to allow for prolonged steroid tapers to manage drug-related AE are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

The assessment for discontinuation of immunotherapy should be made separately from the assessment to discontinue chemotherapy.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

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

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

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

8.1.2 Chemotherapy Dose Discontinuation

Except where specified below, chemotherapy drugs in the PDCT regimen or pemetrexed should be discontinued for any of the following reasons:

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10× ULN for > 2 weeks
  - AST or ALT > 10× ULN
  - TB > 5× ULN
  - Concurrent AST or ALT > 3× ULN and TB > 2× ULN
- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of such drug(s) with the following exception:
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued PDCT dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.

In participants for whom it was indicated that maintenance pemetrexed therapy would be administered, 4 cycles of chemotherapy should be given prior to starting the maintenance treatment. However, participants who experience Grade 4 treatment-related hematologic toxicity or Grade 3 treatment-related non-hematologic toxicity may start maintenance therapy after [redacted] of chemotherapy. The nature and grade of the toxicity must be clearly noted and the Medical Monitor must be notified.

Note: If the investigator is unable to determine whether an AE is due to immunotherapy or PDCT, then all drugs must be discontinued. The assessment for discontinuation of immunotherapy should be made separately from the assessment made for discontinuation of PDCT. If criteria for discontinuation of immunotherapy is met before the 4 PDCT cycles have been completed, then PDCT may continue until 4 cycles have been completed.

A participant in any arm who is discontinued from chemotherapy treatment due to toxicities related to chemotherapy only will remain on the study and continue to receive immunotherapy.

8.1.3 Immunotherapy Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[27]

Participants treated with immunotherapy (nivolumab [± relatlimab]) will be permitted to continue treatment beyond initial RECIST v1.1-defined PD, assessed by the investigator as long as they meet the following criteria:

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

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with immunotherapy.

If the investigator feels that the immunotherapy treated participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities, Table 2-2.

For the participants who continue immunotherapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5-mm absolute increase

from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Immunotherapy treatment should be discontinued permanently upon documentation of further progression.

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

8.1.4 Post-study Treatment Study Follow-up

In this study, ORR and PFS are key efficacy endpoints. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of response outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

If progression as per BICR has not occurred before treatment discontinuation, tumor assessments should continue according to the Schedule of Activities, Table 2-3.

Participants should undergo [redacted] of safety follow-up post last dose of study drug.

[redacted]

8.2 Discontinuation From the Study

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

If a participant specifically withdraws consent for any further contact with him/her or all other persons previously authorized by the participant to provide this information, the following needs to be met.

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

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

8.2.1 Treatment after Discontinuation of the Study

At the conclusion of the study, participants remaining on study treatment who continue to demonstrate clinical benefit may be eligible to receive BMS supplied study drug treatment. Study drug treatment would be provided via a rollover study requiring approval by responsible health authority and IRB/EC or through another mechanism at the discretion of Bristol Myers Squibb.

8.3 Lost to Follow-up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA224104 Imaging Manual provided by the central imaging vendor.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-986016 (relatlimab) and BMS-936558 (nivolumab) IBs.

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

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor. Screening and on-study images should be acquired as outlined in Section 2 Schedule of Activities.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the RECIST v1.1 criteria.

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MR and CT IV contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

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

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response (CR) is identified in target disease or when progression in bone is suspected.

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

MRI of brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue as per the protocol-defined imaging schedule regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (see Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A best overall response of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

9.1.1.3 BICR Confirmation of Progression

Sites should submit all scans to the central imaging vendor on a rolling basis throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor in order for BICR assessment of progression to be performed. The BICR will be completed, and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

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

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2 Patient-reported Outcomes

The evaluation of PROs is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into participant experience that may not be captured through physician reporting.

Participants will be asked to complete the [redacted] the PGIS, and the PGIC at designated study visits. Effective with Protocol Amendment 7, PRO assessments will be completed prior to dosing on Day 1 of each cycle from Cycle 1 (with the exception of the PGIC, which is first completed during Cycle 2) through Cycle 10 and then every other cycle until Cycle 36. For participants in Part 2 only, assessments will continue once every 6 cycles from Cycle 36 until the end of the treatment. Participants in both Parts 1 and 2 will be asked to complete PROs during follow-up Visits 1 and 2 during the long-term follow-up period.

The PROs should be completed in the following order:

[redacted]

2) PGIS
3) PGIC (except for C1D1 when it is not completed)

[redacted]

When possible, participants should complete the PRO measures prior to any other assessments or study procedures when they are being administered during study visits. The questionnaires will be provided in the participant's preferred language. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required.

[redacted]

[redacted]

9.1.2.4 PGIS and PGIC

The PGIS and PGIC will be included as additional exploratory endpoints. The PGIS is a single item that assesses participants' perceptions of overall severity of cancer symptoms for the last 7 days with response options ranging from "none" to "very severe." The PGIC assesses participants' perceptions of overall change in symptom severity since before treatment and assesses whether or not participants feel such a change is meaningful. Response options for this item range from "much worse" to "much improved." Data collected via the PGIS and PGIC will be used as anchor measures to further confirm thresholds for meaningful change for the NSCLC-SAQ.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

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

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

Use CTCAE v5 definitions and grading for safety reporting of all AEs and SAEs on the case reporting form.

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 in the IB represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within [redacted] of discontinuation of dosing. All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until [redacted] following discontinuation of dosing. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

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

All nonserious AEs (not only those deemed to be treatment related) should be collected continuously during the screening period, treatment period and for a minimum of [redacted] following discontinuation of study treatment.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 9.2), and AEs (SAEs and non-serious AEs) associated with confirmed or suspected

SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Union Clinical Trials Regulation 536/2014 and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 7 months after the last dose of chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) or 14 months after the last dose of cisplatin and 5 months after the last dose of immunotherapy, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 6 months after the last dose

of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or 11 months after the last dose of cisplatin administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Adverse Events of Special Interest

9.2.6.1 Definition of Immune-mediated Adverse Events

IMAEs are specific events that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which participants received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs include events, regardless of causality, occurring within [redacted] of the last dose. This list is subject to change based on [redacted] change of MedDRA version. The final list used will be described in the clinical study report (CSR).

Table 9.2.6.1-1 below provides a summary of the IMAE categories and their respective preferred terms. This list is subject to change based on [redacted] or change of MedDRA version. The final list used will be described in the CSR.

Table 9.2.6.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs Included Under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/thyroiditis	Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis

Table 9.2.6.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs Included Under IMAE Category
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphate; AST = aspartate aminotransferase; IMAE = immune mediated adverse event; PT = preferred term.

9.2.7 Laboratory Test Result Abnormalities

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

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

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

9.2.8 Potential Drug-induced Liver Injury

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

9.2.9 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of immunotherapy greater than the planned dose within a 24-hour time period will be considered an overdose.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

See Section 2 Schedule of Activities.

9.4.2 Vital Signs

See Section 2 Schedule of Activities.

9.4.3 Electrocardiograms

See Section 2 Schedule of Activities.

[redacted]

9.4.5 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Local laboratory tests may be used to guide clinical decisions and determine eligibility for dosing once eligibility to participate in this study has been confirmed by central laboratory results.
- A central/local laboratory will perform the analyses and will provide reference ranges for these tests.
- During screening and treatment, unless otherwise indicated in Table 2-1 and Table 2-2, results of clinical laboratory tests must be reviewed prior to dosing.

Clinical safety laboratory assessments are provided in Table 9.4.5-1.

Table 9.4.5-1: Clinical Safety Laboratory Assessments

Hematology Complete Blood Count – [redacted]	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Lymphocyte count	
Platelet count	
Chemistry	
AST ALT Total Bilirubin ALP LDH Creatinine [redacted] Blood urea nitrogen or serum urea Fasting glucose Magnesium (screening, pre-dose, and completion of PDCT)	Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus Amylase - screening only Lipase - screening only [redacted] TSH, free T3 and free T4 - screening TSH Q6W, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Hepatitis B/C (HBV sAG, HCV antibody, or HCV RNA) - screening only	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
FSH screening - only required to confirm menopause in women < age 55	
HIV testing must be performed as per local regulations - screening only. See Appendix 8.	

Abbreviations: ALP = alkaline phosphate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted] FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; HBV sAG = hepatitis B surface antigen; HCV = hepatitis C; HIV = human immunodeficiency virus; HCG = human chorionic gonadotropin; RNA = ribonucleic acid; PDCT = platinum doublet chemotherapy; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

9.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment. Please see Section 7.7.2.1 for additional details.

9.5 Pharmacokinetics

9.5.1 Pharmacokinetics and Anti-drug Antibody (Immunogenicity) Sample Collection and Processing

Serum sample collection for nivolumab and relatlimab PK and anti-drug antibody (ADA) assessments, as well as plasma sample collection for cisplatin, carboplatin, paclitaxel, and pemetrexed in Part 2 will be performed as per detailed schedule provided in Table 9.5.1-1. All on-treatment PK time points are intended to align with days on which study treatment is administered.

Predose samples should be collected within 30 minutes before the start of dose administration. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

For IV administration, the end of infusion (EOI) occurs when the entire nivolumab + relatlimab dose in the infusion bag is administered to the participant. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after EOI. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. If the EOI is delayed to beyond the nominal infusion duration (30 min), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered. Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all pre-dose and EOI-PK samples. Please ensure accurate documentation of the time and date of sample collection.

Samples will be evaluated for development of ADA. Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow-up on suspected immunogenicity related AEs.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Immunogenicity of nivolumab and relatlimab will be assessed per the standard nivolumab and relatlimab immunogenicity analysis plan.

Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Relatlimab and Nivolumab and Pharmacokinetic Sampling Schedule for Chemotherapy Drugs

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time Relative to Start of Infusion (hr:min)	Nivolumab PK Serum Samples	Nivolumab IMG (ADA) Serum Samples	Relatlimab PK Serum Samples	Relatlimab IMG (ADA) Samples	Chemotherapy PK Plasma Samples
Cycle 1 Day 1	Predose[a]	0:00	X	X	X	X	-
	EOI[b]	0:30	X		X		-
	End of chemotherapy infusion[c]	-	-		-		X
Cycle 1 Day 10[d]		216:00	X		X		
Cycle 2 Day 1	Predose[a]	0:00	X	X	X	X	-
	End of chemotherapy infusion[c]	-	-	-	-	-	X
Cycle 3 Day 1	Predose[a]	0:00	X	X	X	X	
Cycle 5 Day 1	Predose[a]	0:00	X	X	X	X	
Cycle 5 Day 1	EOI[b]	0:00	X		X		
Cycle 9 Day 1	Predose[a]	0:00	X	X	X	X	-

Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Relatlimab and Nivolumab and Pharmacokinetic Sampling Schedule for Chemotherapy Drugs

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time Relative to Start of Infusion (hr:min)	Nivolumab PK Serum Samples	Nivolumab IMG (ADA) Serum Samples	Relatlimab PK Serum Samples	Relatlimab IMG (ADA) Samples	Chemotherapy PK Plasma Samples
Every 6 cycles after Cycle 9 Day 1 (eg, C15D1, C21D1, and so on) until end of treatment or maximum of two years of treatment[e]	Predose[a]	0:00	X	X	X	X	

Abbreviations: ADA = antidrug antibody; IMG = immunogenicity; IV = intravenous; PK = pharmacokinetic.

[a] Predose samples should be collected just before starting the infusion (preferably within 30 minutes). However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose.

[b] The end of infusion (EOI) occurs when the entire dose in the infusion bag is administered to the participant. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose remaining in the infusion line after a flush. A PK sample should be taken immediately prior to the EOI, preferably within 2 minutes prior to the EOI. If the EOI is delayed beyond the nominal infusion duration (30 min), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] This sample should be collected at the end of each chemotherapy infusion administration. For example, if a participant is receiving carboplatin + paclitaxel, then collect carboplatin sample at the end of carboplatin infusion, and paclitaxel sample at the end of paclitaxel infusion.

[d] This sample should be collected in conjunction with the biomarker sample.

[e] All PK and IMG samples collected beyond two years of treatment, but prior to PA7 will be analyzed.

9.5.2 Pharmacokinetics and Immunogenicity Sample Analyses

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/anti-drug antibody (ADA) samples.

The serum samples will be analyzed for drugs (nivolumab and relatlimab), anti-nivolumab ADA, and anti- relatlimab ADA, by validated immunoassays. Only samples that are positive for the presence of anti-nivolumab/anti-relatlimab antibodies will be analyzed as appropriate for anti-nivolumab/anti-relatlimab neutralizing activity.

Concentration analyses for nivolumab and relatlimab in serum and chemotherapy drugs (cisplatin, carboplatin, paclitaxel, and pemetrexed) will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity-related AE, etc).

Additionally, residual bioanalytical samples will be archived for up to 20 years after the end of the study or the maximum period allowed by applicable law and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

9.5.3 Pharmacokinetics Analyses

The nivolumab and relatlimab concentrations data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a popPK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model-determined exposures may be used for E-R analyses. Results of popPK and E-R analyses will be reported separately.

The concentration data obtained for the chemotherapies (cisplatin, carboplatin, paclitaxel, and pemetrexed) will be summarized.

9.6 Immunogenicity Assessments

9.6.1 Immunogenicity Analyses

Details regarding immunogenicity sample collection and processing can be found in Section 9.5.

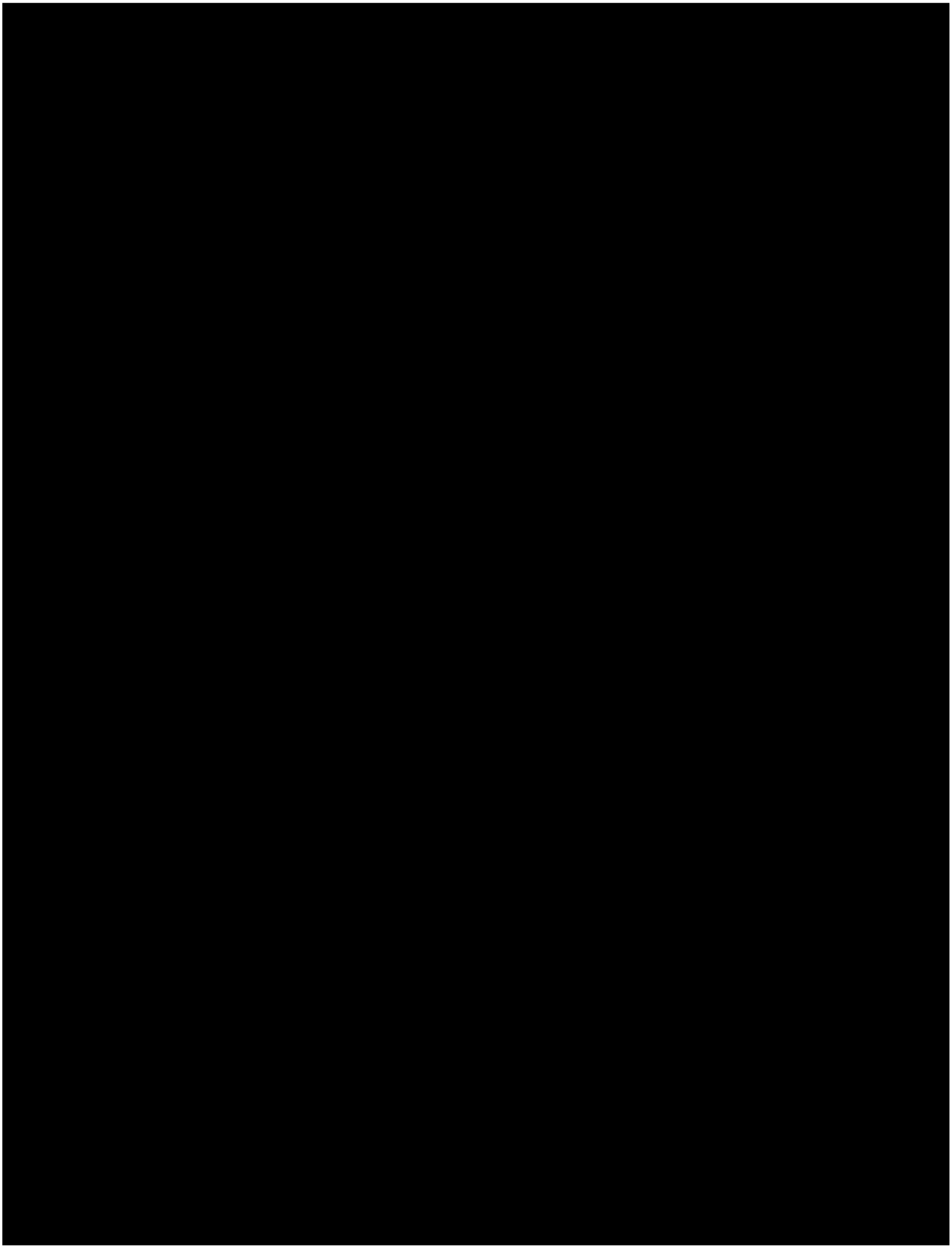
All immunogenicity analyses will be performed using the Immunogenicity Evaluable Participants population. A listing will be provided for all available immunogenicity data. A baseline ADA-positive participant is defined as a participant with positive seroconversion detected in the last sample before initiation of treatment. An ADA-positive participant is a participant with at least 1 ADA positive sample relative to baseline after initiation of the treatment. For each drug, frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment will be summarized. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest

may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

[redacted]

9.9 Biomarkers

[redacted]



[redacted]

9.9.2 Tumor Samples

[redacted] specimens will be obtained from consenting participants prior to treatment to characterize immune cell populations, [redacted] Tumor tissue acquired as a fresh biopsy during screening [redacted] or a recent archived tumor sample [redacted] must be available for submission prior to randomization. Fine needle aspirations or other cytology samples are not acceptable. Submission of on-treatment and upon progression biopsy samples should be collected if medically feasible.

9.9.2.1 Tumor Sample Collection

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain [redacted] samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen; however, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the participant. Detailed instructions of the obtaining, processing, labeling, handling, storing, and shipping of specimens will be provided in a separate Laboratory Manual.

[redacted]

[redacted]

9.9.3 Additional Research Collection

This protocol will include residual sample storage for additional research.

[redacted]

For Non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational Research and Development capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. [redacted]

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.10 Medical Resource Utilization and Health Economics

Healthcare resource utilization will not be collected.

9.11 Clinical Pharmacology Summary

The PK of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab Q2W or Q3W. The geometric mean (% coefficient of variation) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state was 8.0 L (30.4%), and geometric mean elimination half-life was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3 fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The CL of nivolumab increased with increasing body weight. The popPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A popPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate, albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in

combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the CL of ipilimumab. Additionally, popPK and E-R analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the popPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for participants weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Sample Size Determination: Part 1

Up to approximately 120 participants will be randomized 1:1 to treatment Arms A and B (ie, up to 60 participants per arm). [redacted]

10.1.2 Sample Size Determination: Part 2

Approximately 300 participants will be randomized 1:1 (ie, 150 participants per arm) stratified by histology (SQ vs NSQ) and PD-L1 level ($\geq$ 1% [including NQ] vs $<$ 1%). [redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description of Part 2 Populations	Description of Part 1 Populations
All Enrolled Participants	All participants who signed an ICF and were registered in the IRT for Part 2 of the study.	All participants who signed an ICF and were registered in the IRT for the dose safety confirmation part of the study.
All Randomized Participants	All enrolled participants who were randomized to any treatment arm in the study. This population will be used for the efficacy analysis.	Same definition as for Part 2. This population will be used for the (exploratory) efficacy analysis.

Population	Description of Part 2 Populations	Description of Part 1 Populations
All Treated Participants	All randomized participants who received at least 1 dose of any study treatment. Unless stated otherwise, this population will be used for the safety analysis.	Same definition as for Part 2. The primary dose safety confirmation analysis will be based on the Dose-Safety Evaluable Participants (definition below); unless specified otherwise. All Treated Participants will be used for the rest of safety analyses.
Dose-Safety Evaluable Participants	Not applicable	All treated participants in the dose safety confirmation who have completed the safety confirmation period of 12 weeks and have received at least 3 cycles of study drug (including all 4 components: PDCT, nivolumab, and relatlimab), or those who discontinued any study drug due to toxicity prior to completing the safety evaluation period.

Abbreviations: C = cycle; D = day; ICF = informed consent form; IRT = Interactive Response Technology; PDCT = platinum doublet chemotherapy.

10.3 Statistical Analyses

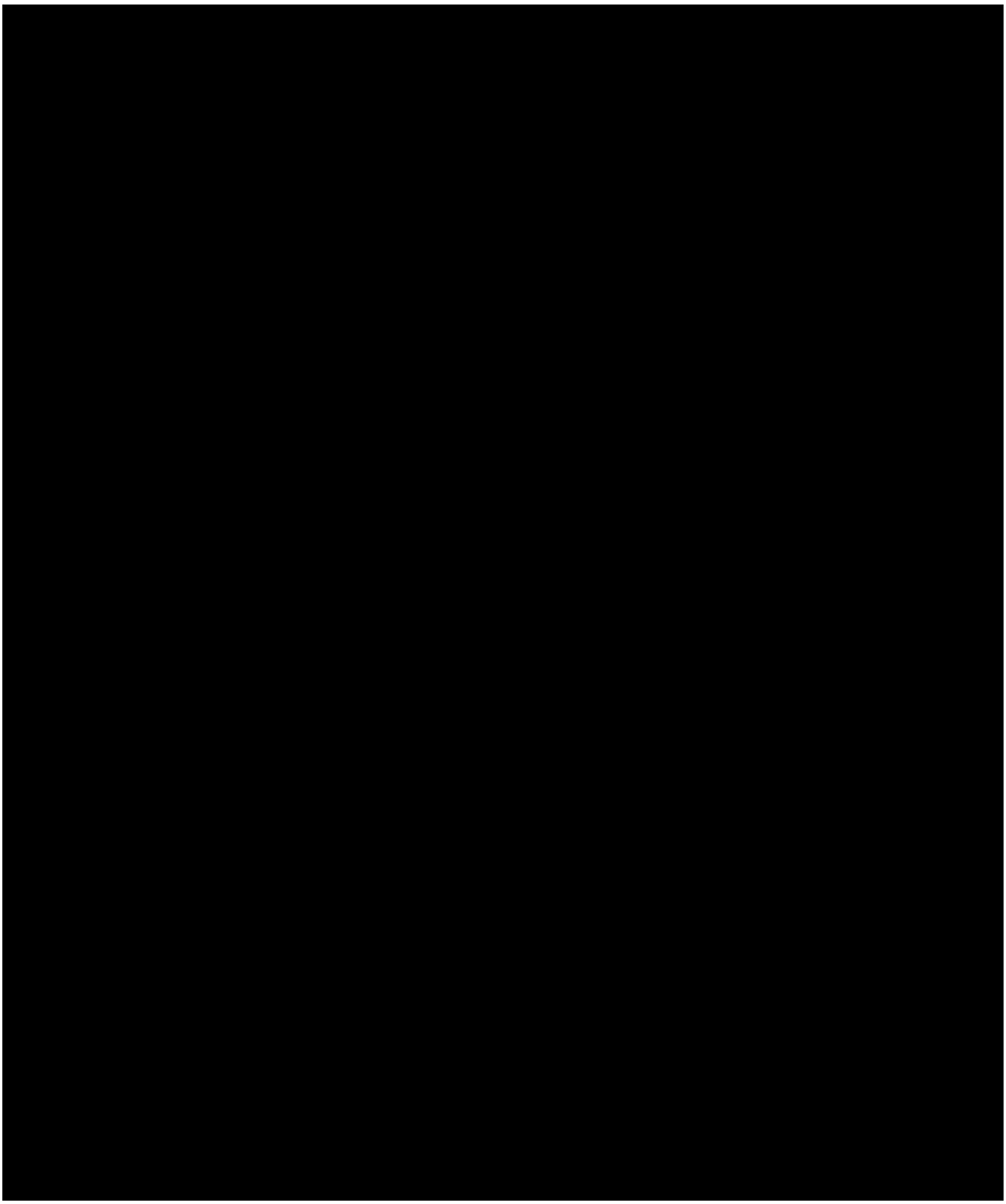
The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

For Part 1, the dose safety confirmation, the analyses of all primary and secondary endpoints are described in Section 10.3.2.

For Part 2, the analyses for the primary and secondary endpoints are described in Section 10.3.1.

- ORR final analysis (Primary analysis): [redacted] No formal hypothesis testing is planned. ORR difference between the two arms and the corresponding 2-sided 90% exact CIs will be included. The difference in ORR will be considered meaningful if the lower bound of the 90% CI is above 0 in favor of the treatment arm. At this analysis, a descriptive analysis of secondary efficacy endpoints will be provided.
- Final analysis for PFS: [redacted] PFS will be estimated using the KM techniques. PFS rates at fixed time points (eg, 6 months, depending on the minimum follow-up) and median PFS will be presented along with their associated 90% CIs. A stratified HR will be calculated using Cox model with the 2-sided 90% CIs will be reported. The PFS benefit may be considered meaningful if the upper bound of the 90% CI for HR is below 1.



10.3.1 Efficacy Analyses

Efficacy endpoints and analyses are described in Table 10.3.1-1 and will be performed on the randomized population.

Table 10.3.1-1: Analysis of Part 2 Primary and Secondary Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Primary: ORR per RECIST v1.1 by BICR ORR is defined as the number of randomized participants with a BOR of CR or PR based on BICR assessments (using RECIST v1.1 criteria) divided by the number of randomized participants for each treatment group. The BOR per BICR is defined as the best overall confirmed response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For participants without documented progression as per BICR 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.	Point estimate and confidence interval will be used to describe ORR. A 2-sided 90% exact CIs for difference of response rates between the treatment groups will be reported. The number and percentage of participants in each category of BOR will be presented by treatment group. Estimates of response rate, along with its exact 2-sided 90% CI [redacted] will be presented by treatment group.
Secondary: PFS per RECIST v1.1 by BICR PFS is defined as the time between the date of randomization and the first date of documented progression, based on BICR assessments (per RECIST v1.1), or death due to any cause, whichever occurs first. Censoring rules for PFS are presented in Table 10.3.1-2.	PFS will be compared between the 2 treatment groups using a stratified HR using Cox model. A 90% CI for HR will also be provided. PFS will be estimated using the KM techniques. PFS rates at fixed time points (eg, 6 months, depending on the minimum follow-up) and median PFS will be presented along with their associated 90% CIs. The estimates will be derived from the KM estimates and corresponding CIs will be derived using the Greenwood formula or Brookmeyer-Crowley method as applicable.
Secondary: PFS per RECIST v1.1 by BICR in subgroups defined by PD-L1 expression, LAG-3 expression, FGL-1 expression PFS is defined the same way as for the primary analysis.	PFS will be estimated using the KM techniques in each subgroup. PFS rates at fixed time points (eg, 6 months, depending on the minimum follow-up) and median PFS will be presented along with their associated 90% CIs. The estimates will be derived from the KM estimates and corresponding CIs will be derived using the Greenwood formula or Brookmeyer-Crowley method as applicable.

[redacted]

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CMH = Cochran-Mantel Haenszel; CR = complete response; FGL-1 = fibrinogen-like protein 1; HR = hazard ratio; KM = Kaplan Meier; LAG-3 = lymphocyte-activation gene 3; ORR = overall response rate; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors[redacted].

Table 10.3.1-2: Censoring Scheme Used in 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
Documented progression per RECIST v1.1	Date of the first documented progression per RECIST v1.1 (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
PD or death after starting subsequent anti-cancer therapy	Date of PD or death	Progressed

Abbreviations: PD=progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; v = version.

10.3.2 Safety Analyses

The assessment of safety will be based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, select AEs, IMAEs, and abnormalities in specific clinical laboratory assessments. See Section 9.2 for details. AEs will be coded using the most current version of the MedDRA. All AEs and laboratory values will be graded for severity according to the NCI CTCAE v5.

Safety endpoints and analyses are described in Table 10.3.2-1 and will be performed on the treated population, unless otherwise specified.

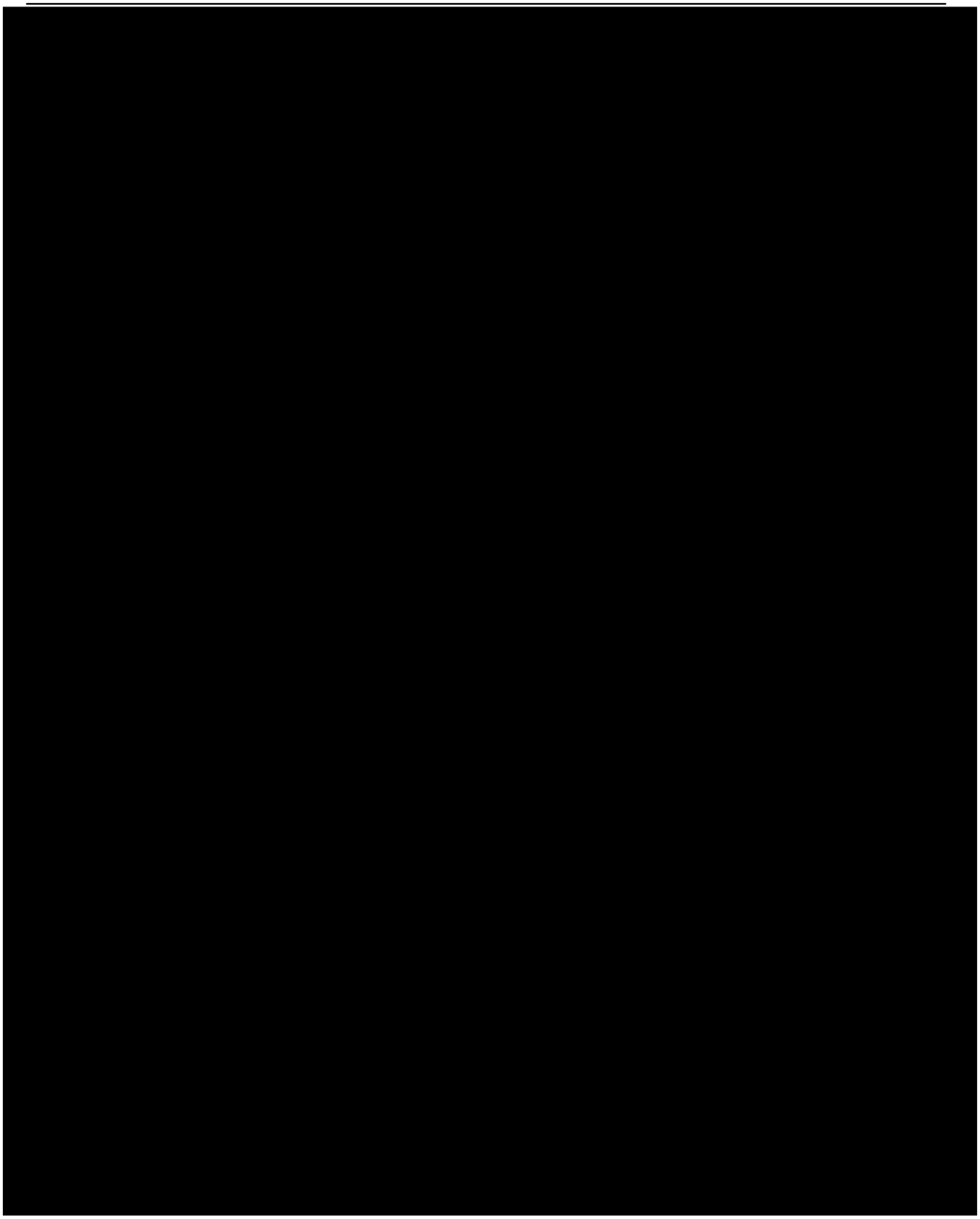
Table 10.3.2-1: Dose Safety Confirmation Primary and Secondary Endpoints

Endpoint	Statistical Analysis Methods
Primary	Within each arm of Part 1, the proportion of participants in the dose-safety evaluable population who had a TRAE leading to discontinuation of any component in the regimen (IO, chemo, or both) within 12 weeks of the first dose will be presented, along with exact 2-sided 90% CI[redacted] for each treatment arm. A 2-sided 95% CI for difference of these rates between the treatment groups will also be computed.
Secondary	Safety and tolerability (incidence of TRAEs leading to discontinuation, AEs, SAEs, and select AEs) will be assessed on all treated participants within Part 1.
[redacted]	

Abbreviations: AE = adverse event; CI = confidence interval; IO = immunotherapy; SAE = serious adverse event; [redacted]; TRAE = treatment related adverse event.

[redacted]

[redacted]



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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first line
ADA	anti-drug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphate
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
[redacted]	[redacted]
AUC	area under the concentration-time curve
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BP	blood pressure
BRAF	B-rapidly accelerated fibrosarcoma proto-oncogene
BTLA	T-lymphocyte attenuator
C	cycle
[redacted]	
CBC	complete blood count
CI	confidence interval
CL	clearance
CLss	steady-state clearance
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CNS	central nervous system

Term	Definition
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CSR	clinical study report
CT	computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
[redacted]	
DC	discontinuation
[redacted]	[redacted]
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
[redacted]	[redacted]
DoR	duration of response
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
EOI	end of infusion
E-R	exposure-response

Term	Definition
ESMO	European Society for Medical Oncology
[redacted]	
FDA	Food and Drug Administration
FDC	fixed dose combination
FGL-1	fibrinogen-like protein 1
[redacted]	
[redacted]	[redacted]
FSH	follicle stimulating hormone
GBS	Guillain-Barre syndrome
[redacted]	[redacted]
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICOS	inducible T-cell costimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
Ig	immunoglobulin
[redacted]	[redacted]
IL	interleukin
[redacted]	[redacted]

Term	Definition
IM	intramuscular
IMAE	immune-mediated adverse event
IMG	immunogenicity
IO	immuno-oncology
IP/IMP	Investigational (Medicinal) Products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
Kd	dissociation constant
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
[redacted]	[redacted]
LVEF	left ventricular ejection fraction
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MHC	major histocompatibility complex
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
[redacted]	[redacted]
Non-IP/Non-IMP	non-investigational (medicinal) products
[redacted]	[redacted]
NSCLC	non-small cell lung cancer

Term	Definition
[redacted]	[redacted]
NQ	non-quantifiable
NSQ	non-squamous
OESI	other events of special interest
OF	O'Brien-Fleming
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PDCT	platinum doublet chemotherapy
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
[redacted]	[redacted]
PFS	progression free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PRO	patient reported outcome
[redacted]	[redacted]
PS	performance status
PT	preferred terms
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
[redacted]	[redacted]
RCC	renal cell cancer

Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
[redacted]	[redacted]
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAV	single agent vial
SC	safety committee
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
[redacted]	
SQ	squamous
t1/2	elimination half-life
TB, T.bili	total bilirubin
TCR	T-cell receptor
[redacted]	[redacted]
TILs	tumor infiltrating lymphocytes
[redacted]	
TRAE	treatment-related adverse event
Treg	T-regulatory cells
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
USPI	US Prescribing Information
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as applicable by the International Council on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines
- in accordance with the ethical principles underlying European Union Clinical Trials Regulation 536/2014
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

Subjects/participants unable to give their written consent (eg, stroke or subjects/participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

SCIENTIFIC PUBLICATIONS

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

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins

from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c] • Bilateral tubal occlusion
• Vasectomized partner Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment.*

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.4 Baseline Documentation Of 'Target' And 'NonTarget' Lesions

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

Table 2.3.2-1: Time Point Response

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

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

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

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

2.3.3 Best Overall Response

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

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

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

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

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

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

2.3.4 Confirmation Scans

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

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

2.4 REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 7 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

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

APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06:

Amendment 06 incorporates the following design changes, [redacted]

- [redacted]
- [redacted]
- [redacted] and the carboplatin dose has been restricted to AUC 5 for non-squamous histology to align with global standard of care and to reduce variation in management of this participant population.[1]

Additionally, the primary and secondary endpoints in Part 2 have been updated to overall response rate (ORR) and progression-free survival (PFS), respectively. ORR is an acceptable Phase 2 endpoint in oncology studies in non-small cell lung cancer (NSCLC) that allows results to be assessed earlier when compared with survival-based endpoints. Furthermore, a strong trial-level association has been established between ORR and PFS in a meta-analysis of advanced NSCLC studies.[2] [redacted]

Other revisions include clarifications to scheduling of safety laboratory, biomarker and pharmacokinetic collections, eligibility criteria, including a revision of the duration of contraception for female participants and male participants and their female partners after last dose of chemotherapy and recommendation to consider treating sub-clinical infection in the presence of elevated neutrophil and white blood cell counts at baseline.

References:

[1] Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. N Engl J Med 2018;378:2078-2092.

[2] Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and participant-level analyses. J Clin Oncol 2015;33:1008-14.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated Medical Monitor contact information Updated study title	To include the most recent study contact. Title updated to reflect the double-blind design
Table 2-1: Screening Procedural Outline	• Added time period for collection of Physical Measurements/PE, ECOG, and Vital signs. • Removal of reference to reconsent per Amendment 03. • PRO collection for Part 2 has been added.	• Clarification of timeframe of collections • Reconsent per Amendment 03 was applicable to participants in Part 1. • Add assessments for Part 2.
Table 2-2: On Treatment Procedural Outline Section 5.1 Overall Design Section 5.1.2 On-treatment Phase Section 5.4.4 Rational for Choice of Chemotherapy Section 7.1.2 Chemotherapy Dosing Table 9.4.5-1 Clinical Safety Laboratory Assessments	[redacted] • Added clarification regarding nab-paclitaxel administration. [redacted]	[redacted]
Table 2-1: Screening Procedural Outline	Added [redacted] PGIS, [redacted] at Screening for Part 2	[redacted]
Table 2-3: Follow-up and Survival Procedural Outline	Additional description of progressive disease assessment removed.	Edited for conciseness as assessment of disease progression is a standard procedure.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.1.1, Research Hypothesis Table 4-1, Objectives and Endpoints Section 5.4.8 Rationale for ORR as a Primary Endpoint in Part 2 Section 8.1.4 Post-study Treatment Study Follow-up	• Updated to reflect ORR as primary endpoint for Part 2. [redacted] • Included rationale for ORR as primary endpoint for Part 2	To update and justify primary and secondary endpoint changes in Part 2.
Table 4.1, Objectives and Endpoints	Removed objectives pertaining to analyzing meaningful change thresholds from both Parts 1 and 2.	[redacted]
Section 2 Schedule of Activities, Table 2-2 On-treatment Procedural Outline [redacted] Figure 5.1-1, Study Design Schematic Section 5.1.2, On-Treatment Phase Section 7. 1, Treatments Administered	Updated relatlimab dose to 360 mg for Part 2.	To clarify the selected relatlimab dose of 360 mg Q3W in combination with nivolumab and PDCT [redacted]
Section 5.1.3 Follow-up Period	Updated to specify tumor and response assessment.	Added for clarity and to ensure adequate follow-up to prevent missing data for secondary objective of PFS.
[redacted]		
Section 5.3 End of Study Definition	Updated the end of study definition.	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
Section 5.4.4, Rationale for Choice of Chemotherapy Section 7.1.2 Chemotherapy Dosing Section 7.1.2.2 Nab-Paclitaxel and Carboplatin Section 7.1.2.4 Pemetrexed and Carboplatin Section 7.4.2 Dose Delay Criteria for Chemotherapy Section 7.4.3.2 Dose Reduction for Chemotherapy Section 7.4.3.3 Chemotherapy Dose Reductions for Hematologic Toxicity Table 7.4.3.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts) Table 7.4.3.4-1 Dose Modifications for Non-hematologic Toxicity	Updated to reflect that nab-paclitaxel for SQ and carboplatin AUC 6 for NSQ is applicable to Part 1 only.	[redacted]
[redacted]		
Section 5.5 Justification for Immunotherapy Dose Section 5.5.2 Justification for Relatlimab Dose	Updated to provide rationale for selection of 360mg relatlimab dose.	To discuss the justification for the selection of relatlimab 360 mg Q3W in combination with nivolumab [redacted]
Section 6.1, Inclusion Criteria, 3) Age and Reproductive Status, ix), (2); b), iv), v), vi), vii), and viii). Section 9.2.5 Pregnancy	Updated total duration of contraception to 7 and 11 months post-last dose of chemotherapy (applicable to paclitaxel, nab-paclitaxel, pemetrexed, and carboplatin) and 14 and 11 months post last dose of cisplatin, whichever is longer, for female participants and male participants and their partners, respectively.	To provide a more precise duration of contraception per label of individual chemotherapy agents.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7, Treatment Table 7-1: Study Treatments for CA224104 Section 7.1 Treatments Administered Section 7.1.1 Immunotherapy Dosing	Mention of placebo has been removed.	[redacted]
Section 9.1.1.3 BICR Confirmation of Progression	Removal of recurrence from the section title.	Recurrence is not applicable in the metastatic setting.
[redacted]		
Section 9.1.2.4 PGIS and PGIC	Removal of assessment of psychometric measurements.	Data collected via the PGIS and PGIC will be used as anchor measures to further confirm thresholds for meaningful change for the [redacted] rather than to assess psychometric measurement properties.
Section 9.5.1 Pharmacokinetic and Anti-drug Antibody Sample Collection and Processing Section 9.5.2 Pharmacokinetics and Immunogenicity Section 9.5.3 Pharmacokinetic Analysis Section 9.6 Immunogenicity Assessments Section 9.6.1 Immunogenicity Analyses	• Schedule and details of PK and immunogenicity assessments updated to separate end of infusion sampling for immunotherapy vs chemotherapy. • Analyses descriptions added to Sections 9.5.2, 9.5.3, and 9.6.	• Updated for clarity. • End of infusion chemotherapy samplings for PK and immunogenicity analyses.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 2: Study Governance Considerations	Added 2 new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security	Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation (EU-CTR) requirements.

[redacted]

[redacted]

[redacted]		
[redacted]		

Overall Rationale for the Protocol Amendment 04, 01-Dec-2021

[redacted]

[redacted]

Stratification factors for randomization in Part 2 have been updated to include Eastern Cooperative Oncology Group (ECOG) performance status in addition to histology and PD-L1 level; gender and LAG-3 expression level have been removed as stratification factors; censoring definition for progression-free survival was updated to align with the clinical program.

The requirements for contraception and pregnancy monitoring have been updated to align with program-wide specifications for relatlimab. The Benefit/Risk section now includes additional information to address COVID-19 vaccinations.

These changes apply to all participants.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol changes listed below have been incorporated into the protocol summary.		
• Title Page	Update of Clinical Scientist	Administrative change.
• Table 2-1, Screening Procedural Outline (CA224104) – Vital Signs	Vitals signs, obtained during screening, are no longer required to be re-obtained within 72 hours prior to randomization.	Clarified expectations regarding collections of vital signs prior to randomization to reduce participant burden.
– [redacted]	[redacted]. In Part 2, LAG-3 levels are no longer required prior to randomization.	[redacted] Gender and LAG-3 are no longer stratification factors in this study.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
– Table Note and Section 7.1.2 Chemotherapy dosing	Investigator is no longer required to decide on chemotherapy treatment based on histology prior to randomization.	Removed language inconsistent with IRT functionality.
• Table 2-2, On-treatment Procedural Outline (CA224104) – Laboratory Tests • Section 3.3 Benefit/Risk • Table 9.4.5-1, Clinical Safety Laboratory Assessments	[redacted]	
	Removed coagulation profile from laboratory requirements.	Removed coagulation profile from the laboratory requirements as it was a typographic error and not required for the study participant population
– Clinical Observations	Evaluations may now occur via virtual telephone assessment, at the investigator's discretion.	The investigator may determine if the clinical observations may be completed as a remote assessment
• Table 2-2, On-treatment Procedural Outline (CA224104): Footnote a	Text of footnote a has been revised to better specify ongoing safety assessments.	Clarification.
[redacted]		

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section, 3.3, Benefit/Risk Assessment • Section 7.7.1, Prohibited and/or Restricted Treatments	Language has been added to address COVID-19 infection precautions included in the study procedures and the designation of the non-live COVID-19 vaccinations as a concomitant medication with no expected interaction with study treatments.	Updated risk/benefit language to add consideration of COVID-19 vaccination during participation in relatlimab and nivolumab clinical trials and to specify COVID-19 vaccines given to participants in this trial are considered a concomitant medication.
• Section 5, Study Design – Figure 5-1 Study Design • Section 5.1, Overall Design • Section 5.1.1, Screening Phase • Section 7.2 , Method of Treatment Assignment • Section 9.8.2.2, LAG-3 and PD-L1 Expression	Stratification factors have been updated to histology, PD-L1, and ECOG performance status. Gender and LAG-3 are no longer stratification factors in this study. PD-L1 non-quantifiable participants will be included in the PD-L1 ≥ 1% stratum. In Part 2, LAG-3 levels are no longer required prior to randomization.	[redacted] LAG-3 has been removed. Gender has been replaced by ECOG on the basis of the higher prognostic value compared with gender. PD-L1 non-quantifiable participants will now be included in the PD-L1 ≥ 1% stratum instead of the PD-L1 < 1% stratum because the prevalence of PD-L1 ≥ 1% within the quantifiable participants is expected to be slightly higher (57%-60%) than of the PD-L1 < 1% group.
• Section 5, Study Design, Figure 5-1 Study Design	For Arm D, the placebo dose has been removed.	The placebo dose will be in alignment with relatlimab dose for Part B. As stated in footnote b, the relatlimab dose 720 mg Q3W will be replaced with 360 mg Q3W if the 720 mg dose is not determined to be safe.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 5.4.8, Rationale for stratification	Stratification factors updated.	Rationale was updated to reflect changes in the stratification factors (Section 5.1)
[redacted]	Text updated to reflect change in stratification factors.	
• Section 6.1, Inclusion Criteria	Criterion 2) Type of Participant and Target Disease Characteristics c) LAG-3 removed to reflect that LAG-3 is no longer stratification factor or needed for randomization in Part 2 of the study.	
[redacted]		

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 6.1, Inclusion Criteria	Criterion 3) Age and Reproductive Status b) Male Participants Updated the duration of contraception for male participants, female partners of males participating in the study, including female partners who are pregnant or breastfeeding to 11 months after the last chemotherapy dose of the male participant's study intervention. Updated the time frame during which male participants must refrain from donating sperm to 11 months after the last chemotherapy dose.	Updated according to the requirements of all chemotherapy agents per label, which is longer than for immunotherapy.
• Section 7.2, Method of Treatment Assignment	Revised text to specify that for participant randomization, [redacted] rather than date of birth is required.	Alignment with IRT functionality.
[redacted]		
• Section 9.2.5, Pregnancy	Changed the duration to report pregnancy from 33 weeks to 14 months after the last dose chemotherapy and 5 months after the last dose of immunotherapy. Increased the reporting period for male participants for sexual activity without a condom from 33 weeks to 11 months.	Updated according to the requirements of all chemotherapy agents per label, which is longer than for immunotherapy.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
• Section 9.5, Pharmacokinetics and Immunogenicity	All occurrences of the word placebo removed from Table 9.5-1, Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab and Relatlimab for All Participants (Part 1 and Part 2). The duration of PK follow up has been capped at 2 years to reflect current clinical experience.	Removal of typographical error. Two years collection is adequate based on a large database of nivolumab and relatlimab PK/IMG data across various studies and indications
[redacted]		
• Section 11, References	References have been updated per changes in Section 3.3 Benefit/Risk, Section 5.4.8, Rationale for Stratification and Section 7.4.3.3, Chemotherapy: Dose Reductions for Hematologic Toxicity.	Reference section updated to align with revised protocol sections.
• Appendix 2, Study Governance Considerations	Language added for the condition of remote monitoring and to reflect BMS policy for dissemination of study information.	Aligned with updated BMS procedures for COVID-19 response and for reporting of study data and dissemination of study information, as incorporated into the standard text for protocols.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Throughout the protocol	Minor editorial and format changes that do not affect content.	

Overall Rationale for the Protocol Amendment 03, 30-Jul-2021

[redacted]

[redacted]

Summary of key changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol changes listed below have been incorporated into the protocol synopsis.		
• Section 2, Schedule of Activities, Table 2-1, Screening Procedural Outline (CA224104) – Eligibility Assessments	Added language describing consent for current and new participants for Protocol Amendment 3	Provide expectations for participant consent for Protocol Amendment 03.
• Section 2, Schedule of Activities, Table 2-2, On-study Procedural Outline (CA224104) – Targeted Physical Examination – Laboratory Assessments, Laboratory Tests – Footnote [redacted]	[redacted]	

[redacted]

Summary of key changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
– Clinical Observations	Added Clinical Observations row.	Aligned laboratory assessments with increased safety monitoring included in Protocol Amendment 03.
• Section 2, Schedule of Activities, Table 2-3: Follow-up and Survival Procedural Outline (CA224102) – AE Assessment	Changed the duration of collection of SAE and non-serious AEs following discontinuation of study treatment from [redacted]	Change made to increase the duration of ~ 5 times study drug half-life and align across protocol sections.
• Section, 3.3, Benefit/Risk Assessment	Updated language to describe recent safety information from the study and resulting safety measures.	These changes were made to align with updated clinical experience.
• Section 5.1.3 Follow-up • Section 7.7.1 Prohibited and/or Restricted Treatments • Section 8.1.4 Post-study Treatment Study Follow-up • Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information • Section 9.2.2 Method of Detecting AE and SAEs • Section 9.2.6.1 Definition of Immune-mediated Adverse Events	[redacted]	The increased safety follow-up of [redacted] represents ~5 times study drug half-life.

Summary of key changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 6.2, Exclusion Criteria 3) Physical and Laboratory Test Findings ii) • Section 7.4.1 Dose Modification Criteria for Immunotherapy, [redacted]	The investigator rather than a cardiologist will now assess [redacted] and benefit-risk for treatment in the study. [redacted]	To avoid unnecessary delays, this change allows the investigator the flexibility to evaluate asymptomatic [redacted] at screening without the need for a cardiologist consultation.
[redacted]		
• Section 9.4.5 Clinical Safety Laboratory Assessments, Table 9.4.5-1 Clinical Safety Laboratory Assessments	Note added to specify that CBC with differential must be evaluated on chemotherapy treatment days for all participants. [redacted] added to laboratory assessments.	Participants placed on nab-paclitaxel will have additional dosing days [redacted] Safety labs (CBC with differential) should be performed in addition to Day 1. To align with increased safety monitoring.

Overall Rationale for the Protocol Amendment 02, 16-Apr-2021

The primary reasons for these changes are to align the immunotherapy dose modification criteria and immune-related adverse event management algorithms with the current Common Terminology Criteria for Adverse Events (CTCAE) version 5; clarify the serologic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and include information of on coronavirus disease 2019 (COVID-19) vaccination and washout periods; clarify the infusion

duration [redacted]; add instructions for location of specific management guidelines for severe adverse reactions; and incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, and sample collections.

In addition, this protocol amendment makes minor clarifications for consistency throughout the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities	• Added language on timing of informed consent and procedures regarding re-enrollment of participants who were considered pre-treatment failures.	• Clarified informed consent note on timing and re-enrollment of participants deemed pre-treatment failures.
	• Added instructions to contact BMS Medical Monitor when participants with significant cardiovascular abnormalities are considered for enrollment.	• Clarified expectations about participants with significant cardiovascular abnormalities and added instructions to inform BMS Medical Monitor when patients with significant abnormalities are considered for enrollment.
	• Referenced study Laboratory Manual for specific tumor collection guidance.	• Clarified requirements and expectations for tumor collections.
	• Added language to indicate that local laboratory testing is the preferred testing for EGFR, ALK, ROS-1, and BRAF V600E mutations status.	• Clarified expectation for local laboratory testing for EGFR, ALK, ROS-1, and BRAF V600E mutation status.
	• Added language for continuous collection of AEs/SAEs (including those associated with SARS-CoV-2 infection) during the treatment period.	• Clarified expectations about continuous collection of AEs/SAEs, including those associated with SARS-CoV-2 infection, during the treatment period.
	• Removed language instructing the regrading of	• Updated language to reflect new immunotherapy dose modification section and immune-related adverse

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	AEs to CTCAE v4 for management.	event (irAE) management algorithms that align with CTCAE v5.
	• Added additional time points for collection of SARS-CoV-2 serology.	• Clarified expectations on SARS-CoV-2 serum collections and use of results for eligibility.
	• Added or updated details to Notes columns for [redacted] and body imaging.	• Updated or corrected Notes as needed to clarify expectations and/or to better align with protocol text.
[redacted]		
Section 1: Synopsis Section 5: Study Design; Figure 5.1-1	Updated Figure 5.1-1; deleted term, or 2 years in diagram.	Corrected typographical error, as study treatment is until PD or unacceptable toxicity.
Section 5.1.1: Screening Phase	• Clarified language on allowable time from biopsy to 3 months prior to randomization.	• Updated wording to clarify that timeline is from randomization, not from enrollment.
	[redacted]	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.4.3: Rationale for Shortened Infusion Time for Nivolumab plus Relatlimab	Added language clarifying the extended infusion time [redacted] to maintain endotoxin specifications.	Added clarification to align with the Pharmacy Manual.
Section 5.5.1: Justification for Nivolumab Dose	Updated language on standard of care.	Deleted pembrolizumab plus chemotherapy as the standard of care, as other treatments have been approved.
Section 5.5.2: Justification for Relatlimab Doses	Updated text and added language with more recent data and added PK/pharmacodynamic information on relatlimab and nivolumab.	Added updated data regarding the PPK model that predicts receptor occupancy.
Section 5.6: Clinical Pharmacology	Added text on the clinical pharmacology of relatlimab and nivolumab.	Added description of the clinical pharmacology of nivolumab and relatlimab.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Synopsis Section 6.1: Inclusion Criteria	Criterion 2) c) i) and Key Inclusion Criteria: added text to reference the Laboratory Manual for additional information on tumor collection.	Referenced Laboratory Manual for additional information on tumor collection.
Section 6.2: Exclusion Criteria	The following changes were made: • Criteria 1) c, d, e, and g): adjusted time frames to reflect up to participant randomization. • Criterion 1) h): added text to clarify requirements for participation of participants who are HIV positive. • Criterion 1) n): was removed and Criterion 1) o) text was added for participants with previous exposure to SARS-CoV-2. • Criterion 2) h): was added for participants currently in other investigational trials, including those for COVID-19. • Criterion 3) b) ii): text was added regarding retesting of [redacted] cardiac consultation, and notification of BMS Medical Monitor.	Changed to clarify timing of specific exclusion criteria and to include new clinical approaches for previous exposure to viral infections, washout period, participants in other investigational trials, and laboratory tests.
Section 6.4.1: Retesting During Screening or Dose Safety Confirmation Period	Added text describing testing and retesting of participants who may develop suspected or confirmed symptomatic COVID-19 during the screening period.	Clarified expectations for eligibility and retesting of participants with suspected or confirmed symptomatic COVID-19.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1: Immunotherapy Dosing	Added text to clarify extended infusion times of immunotherapy dosing [redacted]	Clarified infusion times based on participant weight and aligned with Pharmacy Manual.
Section 7.1.2.3: Pemetrexed and Cisplatin	Updated duration of chemotherapy treatment to 4 cycles.	Corrected typographical error to clarify the correct duration of chemotherapy treatment.
Section 7.2: Method of Treatment Assignment	Removed the following criteria for participant randomization: • Will participant be treated with cisplatin, if eligible (NSQ participants only)? • Will participant be treated with nab-paclitaxel, if eligible (SQ participants only)? • Will participant be treated with pemetrexed maintenance, if eligible (NSQ participants only)?	Clarified IRT functionality, as it does not capture chemotherapy regimens as part of the required randomization criteria.
Section 7.4.1: Dose Modification Criteria for Immunotherapy; Section 7.4.2: Dose Delay Criteria for Chemotherapy; Section 7.4.3.3: Chemotherapy: Dose Reductions for Hematologic Toxicity; Section 7.4.3.4: Chemotherapy: Dose Reductions for Non-	Updated criteria for immunotherapy dose delay, resumption, and discontinuation. Added suspected or confirmed SARS-CoV-2 infection as a criterion to delay treatment as well as criteria for resumption of treatment. Added [redacted] modifying text from prior paragraph format.	Updated dose delay, resumption and discontinuation criteria to align with the current CTCAE v5. Updated dose delay criteria to include expectations in cases of suspected or confirmed SARS-CoV-2 infection and criteria for resumption of treatment. Combined criteria for delay, resumption, and discontinuation of immunotherapy into a table to facilitate access and comprehension.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
hematologic Toxicities; Section 7.4.4: Criteria to Resume Dosing; Section 7.4.6: Treatment of Immunotherapy Infusion Reactions; Section 8.1.1: Immunotherapy Dose Discontinuation; Section 9.2: Adverse Events		
Section 7.4.2: Dose Delay Criteria for Chemotherapy; Table 7.4.3.4-1 Dose Modifications for Non-hematologic Toxicity	Added text clarifying that dose modification guidance from local chemotherapy labels may vary from USPI.	Clarified that management of chemotherapy adverse events per local label is allowed.
Table 7.4.3.3.-1 Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)	Updated text to clarify window of Grade 3 platelet levels.	Updated to aid in reading comprehension.
Section 7.4.4.2: Criteria to Resume Treatment with Chemotherapy	Updated criteria to resume chemotherapy for ANC and platelet counts.	Corrected typographical errors.
Section 7.7.1: Prohibited and/or	Added text on COVID-19 vaccination, washout period,	Clarified guidance regarding COVID-19 vaccines as concomitant therapy.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Restricted Treatments	and prohibition of use after last study drug treatment.	
Section 8.1.3: Immunotherapy Treatment Beyond Disease Progression	Updated language from "nivolumab" to "immunotherapy."	Corrected typographical errors.
Section 9.1.2: Patient-reported Outcomes	Added language on completion of the PRO measures in the participant's preferred language as well as use of alternate administration methods.	Clarified expectations for administration of PRO evaluations in extenuating circumstances.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Updated IB section where Reference Safety Information is found.	Corrected typographical error for location of Reference Safety Information in relevant relatlimab and nivolumab IB and chemotherapy treatments.
	Added text to describe collection of all AEs and SAEs in the context of SARS-CoV-2 infection.	Included language for AE/SAE collection in the context of SARS-CoV-2 infection.
Section 9.2.3: Follow-up of AEs and SAEs	Updated language to include follow-up of SAEs and nonserious AEs associated with confirmed or suspected SARS-CoV-2 infection.	Included language for collection of AE/SAE events in the context of SARS-CoV-2 infection and the duration of the follow-up.
[redacted]		
Section 9.4.5: Clinical Safety Laboratory Assessments	Added text to Table 9.4.5-1 • Chemistry: modified magnesium collection to screening, pre-dose, and completion of PDCT	Clarified assessments related to magnesium.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5: Pharmacokinetics and Immunogenicity	• Added text to clarify the collection of PK time points and alignment with study treatment days. • Table 9.5-1: Modified table to reflect the Placebo collection.	Changed to clarify timing and alignment PK sample collection with study treatment days.
[redacted]		
All	Made minor formatting and typographical corrections.	Because these changes are minor, they have not been summarized.

Overall Rationale for the Protocol Amendment 01, 11-Nov-2020

Protocol Amendment 01 is being implemented to incorporate two key changes that 1) clarify the inclusion/exclusion criteria and 2) align the concomitant medications section with the US product label of the chemotherapy agents to be administered as part of the study drug regimen.

Summary of key changes of Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	Exclusion criteria 3.h) serum creatinine; the creatinine clearance (CrCl) value was changed to >50mL/min (measured or calculated using the Cockcroft-Gault formula)	The renal function eligibility criterion was modified to comply with label restrictions of pemetrexed and to avoid the risk of enrolling participants with borderline allowable CrCl levels who may need to be discontinued from cisplatin within a short period of time.
Section 7.7.1 Prohibited and/or Restricted Treatments	Added the words "drug interactions" to the language describing investigator adherence to USPI or local label for each one of the chemotherapy agents.	Modified the concomitant medication instructions to reference the drug interaction information in the USPI for the relevant chemotherapy agents.