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Clinical Protocol CA2099LA

A Study of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

(CheckMate 9LA, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9LA)

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	10-May-2017	Not applicable

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
TABLE OF CONTENTS 4
1 SYNOPSIS 8
2 SCHEDULE OF ACTIVITIES 12
3 INTRODUCTION 19
[redacted]
4 OBJECTIVES AND ENDPOINTS 26
5 STUDY DESIGN 27
5.1 Overall Design 27
5.1.1 Data Monitoring Committee and Other External Committees 29
5.1.1.1 Data Monitoring Committee 29
5.1.1.2 Blinded Independent Radiology Central Review 30
5.2 Number of Participants 30
5.3 End of Study Definition 30
[redacted]
6 STUDY POPULATION 41
6.1 Inclusion Criteria 41

6.2 Exclusion Criteria 43
6.3 Lifestyle Restrictions 44
6.4 Screen Failures 45
6.4.1 Retesting During Screening Period 45
7 TREATMENT 45
7.1 Treatments Administered 47
7.1.1 Dosing 48
7.1.1.1 Nivolumab and Ipilimumab Dosing for Treatment Arm 48
7.1.1.2 Chemotherapy Dosing 48
7.1.1.3 Optional Continuation-Maintenance 51
7.1.2 Treatment of Nivolumab or Ipilimumab Infusion Reactions 52
7.1.3 Treatment Beyond Disease Progression 53
7.2 Method of Treatment Assignment 54
7.3 Blinding 55
7.4 Dosage Modification 55
7.4.1 Dose Delay Criteria 55
7.4.1.1 Dose Delay Criteria for Nivolumab and Ipilimumab 55
7.4.1.2 Dose Delay Criteria for Chemotherapy 56
7.4.2 Dose Reductions 57
7.4.2.1 Dose Reduction for Nivolumab or Ipilimumab 57
7.4.2.2 Dose Reduction for Chemotherapy 57
7.4.2.3 Dose Reductions for Hematologic Toxicity 58
7.4.2.4 Chemotherapy - Dose Reductions for Non-Hematologic Toxicities 59
7.4.3 Criteria to Resume Dosing 59
7.4.3.1 Criteria to Resume Nivolumab Dosing 59
7.4.3.2 Criteria to Resume Ipilimumab Dosing 60
7.4.3.3 Criteria to Resume Treatment with Chemotherapy 61
7.5 Preparation/Handling/Storage/Accountability 61
7.5.1 Retained Samples for Bioavailability / Bioequivalence 62
7.6 Treatment Compliance 62
[redacted]
7.8 Treatment After the End of the Study 64
8 DISCONTINUATION CRITERIA 64
8.1 Discontinuation from Study Treatment 64
8.1.1 Nivolumab Dose Discontinuation 65
8.1.2 Ipilimumab Dose Discontinuation 66
8.1.3 Chemotherapy Dose Discontinuation 68
8.2 Discontinuation from Study 69
8.2.1 Post Study Treatment Study Follow-up 70
8.3 Lost to Follow-Up 70

9 STUDY ASSESSMENTS AND PROCEDURES 70
9.1 Efficacy Assessments 71
9.1.1 Methods of Measurements 71
9.1.2 Imaging and Clinical Assessment 72
9.1.2.1 Assessment of Baseline Tumor Assessment 72
9.1.2.2 BICR Assessment of Progression 72
9.1.3 Study Outcomes Research Assessments 73
9.2 Adverse Events 73
9.2.1 Time Period and Frequency for Collecting AE and SAE Information 73
9.2.2 Method of Detecting AEs and SAEs 74
9.2.3 Follow-up of AEs and SAEs 74
9.2.4 Regulatory Reporting Requirements for SAEs 75
9.2.5 Pregnancy 75
9.2.6 Adverse Events of Special Interest 75
9.2.7 Laboratory Test Result Abnormalities 76
9.2.8 Potential Drug Induced Liver Injury (DILI) 77
9.2.9 Other Safety Considerations 77
9.3 Overdose 77
9.4 Safety 77
9.4.1 Physical Examinations 77
9.4.2 Vital signs 77
9.4.3 Clinical Safety Laboratory Assessments 77
9.4.4 Imaging Safety Assessment 78
9.4.5 Electrocardiogram (ECG) 78
[redacted]
10 STATISTICAL CONSIDERATIONS 85
10.1 Sample Size Determination 85

10.2 Populations for Analyses 85
10.3 Statistical Analyses 86
10.3.1 Efficacy Analyses 86
10.3.1.1 Methods for Primary Endpoints 87
10.3.1.2 Methods for Secondary Endpoints 87
10.3.2 Safety Analyses 88
[redacted]
10.3.4 Patient Reported Outcomes Analyses 89
10.3.4.1 Outcomes Research Analyses 89
10.3.5 Other Analyses 89
10.3.6 Interim Analyses 89
[redacted]

1 SYNOPSIS

Protocol Title: A Study of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer (NSCLC)

Study Phase: Phase 3

[redacted]

Study Population:

- Participants with histologically confirmed stage IV non-small cell lung cancer (NSCLC), squamous or non-squamous histology. (Defined by the 7th International Association for the Study of Lung Cancer Classification)
- No prior systemic therapy for stage IV disease.
- EGFR/ALK wild type and ECOG Performance Status of ≤ 1
- Participants are to have tumor tissue sample for biomarker analysis
- Participants must have PD-L1 IHC testing with results available for randomization or PD-L1 testing will be performed by the central laboratory during the screening period.

Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy of nivolumab + ipilimumab with chemotherapy vs chemotherapy in participants with histologically confirmed stage IV NSCLC	• Overall survival (OS)
Secondary • To compare the efficacy of nivolumab + ipilimumab combined with chemotherapy vs chemotherapy in	• Progression free survival (PFS) by blinded independent central review

Objectives and Endpoints

Objectives	Endpoints
participants with histologically confirmed stage IV NSCLC	• Objective response rate (ORR) by blinded independent central review (BICR)
• To evaluate efficacy outcomes in participants with histologically confirmed stage IV NSCLC treated with nivolumab + ipilimumab combined with chemotherapy vs chemotherapy with different PD-L1 expression levels	• ORR and PFS by blinded independent central review and OS in participants with different PD-L1 levels
• To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as ORR, PFS and OS) of nivolumab + ipilimumab in combination with chemotherapy using DNA derived from tumor and blood (germline) specimens.	• Tumor cell total somatic mutation numbers and their association with ORR, PFS, and OS
[redacted]	

Overall Design

Treatment arm: Nivolumab administered IV and ipilimumab administered IV and 2 cycles of histology-based platinum doublet chemotherapy as induction treatment, followed by nivolumab and ipilimumab until disease progression or unacceptable toxicity. Treatment with nivolumab and ipilimumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment with nivolumab and ipilimumab could be re-initiated as per the initial schedule

for subsequent disease progression (which occurred during the off-treatment period) and administered for up to 1 additional year.

The 2 cycles of histology-based platinum doublet chemotherapy in the treatment arm during induction are the same chemotherapy regimens as in the control arm:

- Squamous histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2
- Non-squamous histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2. The investigator must decide prior to randomization whether or not the participant with non-squamous histology will receive cisplatin, if eligible.

Control arm: 4 cycles of histology-based platinum doublet chemotherapy.

- Squamous histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2
- Non-squamous histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2. The investigator must decide prior to randomization whether or not the participant with non-squamous histology will receive cisplatin, if eligible.
- Chemotherapy will be on day 1 of each 3 week cycle; participants with non-squamous histology who have stable disease or response after induction chemotherapy are permitted to receive optional pemetrexed maintenance therapy: 500 mg/m^2 pemetrexed on day 1 of each 3 week cycle until disease progression or unacceptable toxicity, or other reasons specified in the protocol.

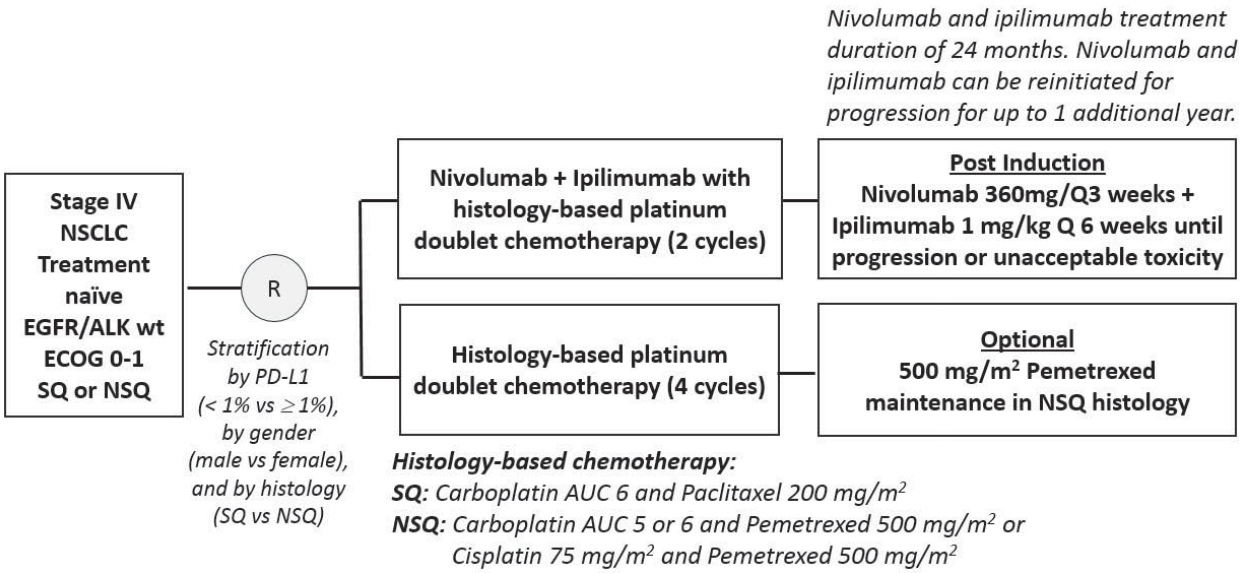
Number of Participants:

Approximately 420 participants will be randomized to treatment arm and control arm in a 1:1 ratio.

Study treatment:

Study Drugs for CA2099LA		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IP
Ipilimumab	5 mg/ml	IP
Carboplatin	10 mg/ml	IP
Paclitaxel	6 mg/ml	IP
Pemetrexed	500 mg/vial	IP
Cisplatin	100 mg/vial (1 mg/mL)	IP

Study Schema for CA2099LA



2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099LA)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed prior to first dose
Medical History	X	
Safety Assessments		
Physical Measurements/Physical Examination	X	Include height and weight. Within 28 days prior to first dose
[redacted]	[redacted]	[redacted]
Vital Signs and Oxygen Saturation	X	Including BP, HR, and temperature. Obtain at the screening visit and within 72 hours prior to first dose
Assessment of Baseline Signs and Symptoms	X	Within 14 days prior to first dose
Serious Adverse Event Assessment	X	Serious Adverse Events from time of consent.
[redacted]	[redacted]	[redacted]
Pregnancy Test (WOCBP only)	X	Within 24 hours prior to Day 1. 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).
Laboratory Tests	X	Must be performed within 14 days prior to randomization: • CBC w/differential • Chemistry panel including: AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, phosphate, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, • Thyroid panel including TSH, Free T4, Free T3 • Hep B/C (HBV sAg, HCV antibody or HCV RNA) within 28 days prior to first dose. • Testing for HIV must be performed as per local regulations.
ECG (12-lead)	X	Obtained only for participants who have met all eligibility criteria

Table 2-1: Screening Procedural Outline (CA2099LA)

Procedure	Screening Visit	Notes
Efficacy Assessments		
Radiographic Tumor Assessments (chest, abdomen, pelvis, brain)	X	Performed within 28 days prior to first dose. CT of chest, abdomen and pelvis, and MRI of brain (to rule out brain metastases) and all known or suspected sites of disease should be assessed at baseline. Radiographic tumor assessments for pelvis must be performed as per local regulations.
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
IWRS /Clinical Drug Supplies		
IWRS	X	For participant number assignment at the time informed consent is obtained

Note: The screening period is 28 days. Any tests/images outside 28 days will need to be repeated. Tumor tissue is to be collected within 3 month prior to enrollment.

Table 2-2: On Study Assessments Treatment Phase- Nivolumab+ Ipilimumab with Platinum-based Doublet Chemotherapy Combination vs Chemotherapy

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Notes 1 Cycle = 3 weeks
Safety Assessments				
Physical Measurements and ECOG Performance Status	X	X		See Appendix 5
Vital Signs and Oxygen Saturation	X	X		
Adverse Event Assessments	Continuously during the study			SAEs should be approved in RAVE within 5 days from entry.
Review of Concomitant Medications	X	X		
Pregnancy Test (WOCBP only)	X	X		To be evaluated at least every 3 weeks
Laboratory Assessments				
Chemistry and hematology tests	X	X	X(TSH)	Within 72 hrs. prior to dosing to include • CBC w/ differential, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, • Thyroid Function Testing TSH (with reflexive Free T4 and Free T3) to be evaluated every 6 weeks Note: C1D1 labs do not need to be repeated if they were performed within 14 days of dosing.
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]

Table 2-2: On Study Assessments Treatment Phase- Nivolumab+ Ipilimumab with Platinum-based Doublet Chemotherapy Combination vs Chemotherapy

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Notes 1 Cycle = 3 weeks
Efficacy Assessments				
Radiographic Tumor Assessment (CT of chest, abdomen, pelvis/MRI of brain)	FIRST tumor assessment should first be performed at 6 weeks (± 7 days) from first dose date. SUBSEQUENT tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months (Week 48), then every 12 weeks (± 7 days) until BICR confirmed disease progression, lost to follow-up, or withdrawal of consent. Tumor assessments should continue after maximum of 24 months of treatment is reached. Participants with a history of brain metastasis must have mandatory surveillance MRI approximately every 12 weeks (± 7 days) from the date of first dose, or sooner if clinically indicated. Radiographic tumor assessments for pelvis must be performed as per local regulations.			
[redacted]				
[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]
Outcomes Assessments				
Patient Reported Outcomes (PRO) Assessment	X	X	After 6 months	For C1D1, LCSS and EQ-5D assessments performed after randomization PRIOR to first dose (day -3 to +1). For On-Study visits: assessments (LCSS and EQ-5D) will be performed PRIOR to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period
[redacted]		[redacted]		[redacted]
Clinical Drug Supplies				
IWRS Vial Assignment	X	X		Within 1 day prior to dosing
Treatment Arm	X	X		Nivolumab + ipilimumab + platinum-doublet chemotherapy (q3 weeks) for 2 cycles followed by nivolumab 360mg

Table 2-2: On Study Assessments Treatment Phase- Nivolumab+ Ipilimumab with Platinum-based Doublet Chemotherapy Combination vs Chemotherapy

Procedure	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Days)	Every 2 Cycles Day 1 (± 3 Days)	Notes 1 Cycle = 3 weeks
Nivolumab + ipilimumab + platinum-doublet chemotherapy (q3 weeks) for 2 cycles followed by nivolumab q3 weeks + ipilimumab q6 weeks		(see note)		q3weeks and ipilimumab 1mg/kg q6 weeks until progression or maximum 24 month treatment duration)
Control Arm Platinum-doublet chemotherapy q 3w x4 cycles with optional pemetrexed maintenance for non-squamous histology	X	X		3 weeks per cycle x4 Non-squamous histology may have option of pemetrexed maintenance therapy until progression or unacceptable toxicity

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) continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure.
2) During retreatment upon progression (with post maximum 24 month therapy), laboratory and tumor assessment schedules will be the same. No PK/PRO collection are required.
3) 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.

Table 2-3: Follow-up and Survival Procedures (CA2099LA) - All participants

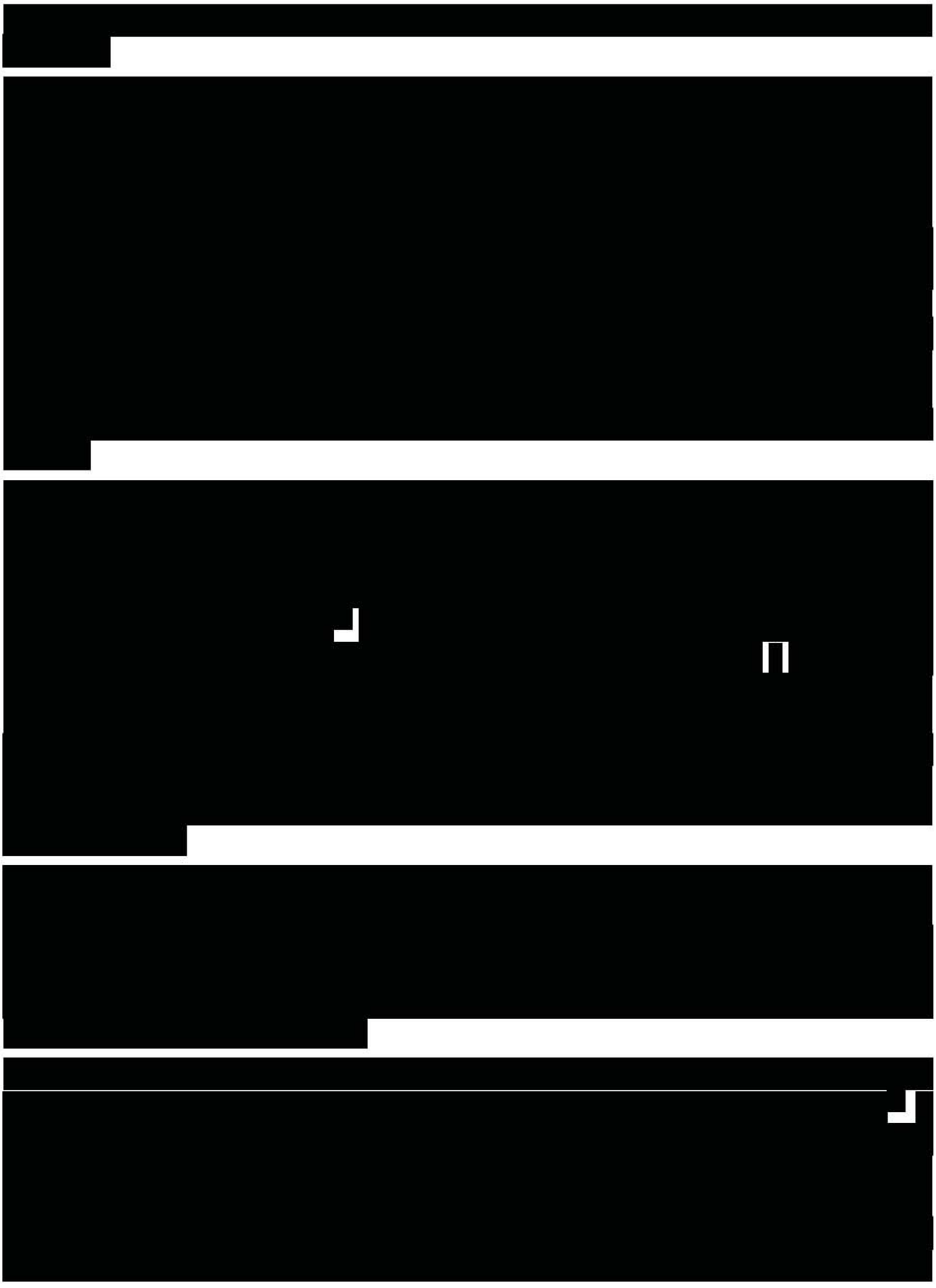
Procedure	Follow-Up Visits 1 & 2[a]	Survival Follow-up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues.
Vital Signs	X		
Adverse Event Assessment	X	X	SAEs should be approved in RAVE within 5 days from entry.
[redacted]	[redacted]		
Laboratory Tests	X		Required at Visit 1. Repeat at Visit 2 only if study drug related toxicity persists.
Pregnancy Test (WOCBP only)	X		
Efficacy Assessments			
Radiographic Tumor Assessment (CT of chest, abdomen and pelvis and known sites of disease)	X	X	For participants who discontinue study treatments for reasons other than PD, follow up scans should be performed every 6 weeks (± 7 days) up to first 12 months (Week 48), then every 12 weeks (±7days) until BICR confirmed PD, lost to follow-up, or withdrawal of consent. Radiographic assessments for participants who have not experienced BICR confirmed PD ***must*** be obtained every 6 weeks (± 7 days) and ***not*** delayed until follow-up visits 1 & 2.
Patient Reported Outcomes Assessment (PRO)	X	EQ-5D only	Both the LCSS and EQ-5D will be collected in FU Visits 1 & 2. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-Up phase, then every 6 months thereafter.
Collection of Survival Status and Subsequent Therapy Information	X	X	Collect **every 3 months** in Survival Visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.

NOTES:

a Follow-up visit 1 (FU1) should occur 35 days from the last dose (± 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up visit #2 (FU2) occurs approximately 115 days (± 7 days) from last dose of study drug. Both Follow Up visits should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit 2. Survival visit may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the subject has withdrawn consent for all contact. If retreatment starts, then follow-up visits will cease.

[redacted]



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4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy of nivolumab + ipilimumab combined with chemotherapy vs chemotherapy in participants with histologically confirmed stage IV NSCLC	• OS
Secondary • To compare the efficacy of nivolumab + ipilimumab combined with chemotherapy vs chemotherapy in participants with histologically confirmed stage IV NSCLC	• PFS by BICR • ORR by BICR
• To evaluate efficacy outcomes in participants with histologically confirmed stage IV NSCLC treated with nivolumab + ipilimumab combined with chemotherapy vs chemotherapy with different PD-L1 expression levels	• ORR and PFS by BICR and OS in participants with different PD-L1 levels

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as ORR, PFS and OS) of nivolumab + ipilimumab in combination with chemotherapy using DNA derived from tumor and blood (germline) specimens.	• Tumor cell total somatic mutation numbers and their association with ORR, PFS, and OS
[redacted]	[redacted]

5 STUDY DESIGN

5.1 Overall Design

Adults (≥ 18 years) male and female participants, with stage IV NSCLC, previously untreated for advanced disease are eligible for enrollment, irrespectively of PD-L1 expression. Tumor tissue is required for study enrollment.

Participants will be assessed by PD-L1 expression, and categorized into 3 groups (PD-L1 positive, PD-L1 negative, and PD-L1 not quantifiable). PD-L1 status will be determined by Dako PD-L1 IHC 28-8 pharmDx test for immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample.

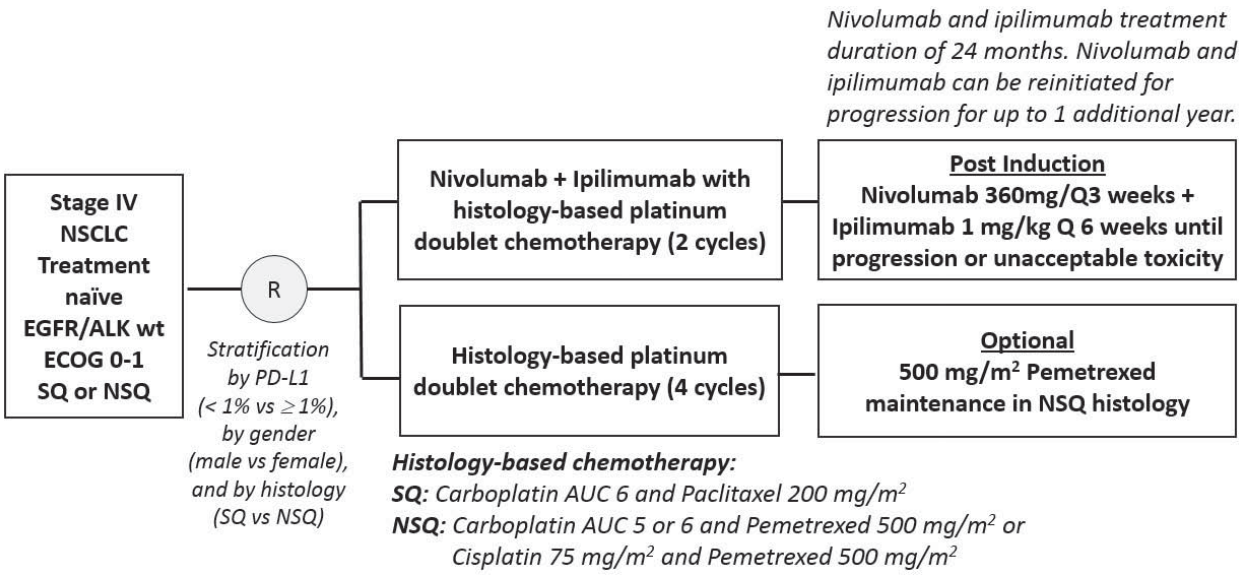
- PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)

- PD-L1 negative (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- PD-L1 not quantifiable (participants with tumor biopsy specimens without quantifiable PD-L1 expression)

Participants are to have tumor tissue sample available for PD-L1 IHC testing performed by a central laboratory during screening period. PD-L1 status is required for randomization.

The enrollment will end when approximately 420 patients are randomized. IWRS will be used to track the enrollment number. Testing of PD-L1 through a central laboratory is required prior to randomization. Participants tested but with not quantifiable PD-L1 will stratify with PD-L1 negative participants. PD-L1 not quantifiable population will be capped to 10% of total randomized population. The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Approximately 420 participants will be randomized in a 1:1 ratio to the treatment arm or control arm. The stratification factors for randomization are PD-L1 level (≥ 1% vs < 1%), histology (squamous vs non-squamous histology), and gender (male vs female). Participants without quantifiable PD-L1 status can be stratified with PD-L1 < 1% population and capped to 10% of the total randomized participants.

The investigator must decide prior to randomization if participant with non-squamous histology will receive cisplatin therapy, based on cisplatin eligibility criteria.

Treatment Arm: Nivolumab will be administered with ipilimumab, plus 2 cycles of histology-based platinum doublet chemotherapy:

- Squamous histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2
- Non-squamous histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

5.1.1 Data Monitoring Committee and Other External Committees

5.1.1.1 Data Monitoring Committee

A DMC will be utilized to provide general oversight and safety considerations for this study CA2099LA. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab/ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety data for the study.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group 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 DMC responsibilities and procedures will be specified in the DMC charter.

5.1.1.2 Blinded Independent Radiology Central Review

Tumor assessments for each participant should be submitted to the radiology vendor as will be performed on an ongoing basis. At the time of investigator-assessed initial radiographic progression per RECIST 1.1 in any given participant, the site must request the Independent Central Review from the third party radiology vendor for confirmation of progression. The blinded, independent radiologists will review all available tumor assessments for that given participant and determine if RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given participant met RECIST 1.1 criteria for progression will be provided to the site. Participants whose disease progression is not confirmed centrally will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the participant to have met RECIST 1.1 criteria for progression.

BICR will review tumor images in all treated participants to determine RECIST 1.1 response for analyses of ORR or PFS. Details of the BICR procedures will be specified in the imaging manual.

5.2 Number of Participants

Approximately 420 participants will be randomized to treatment arm and control arm in a 1:1 ratio.

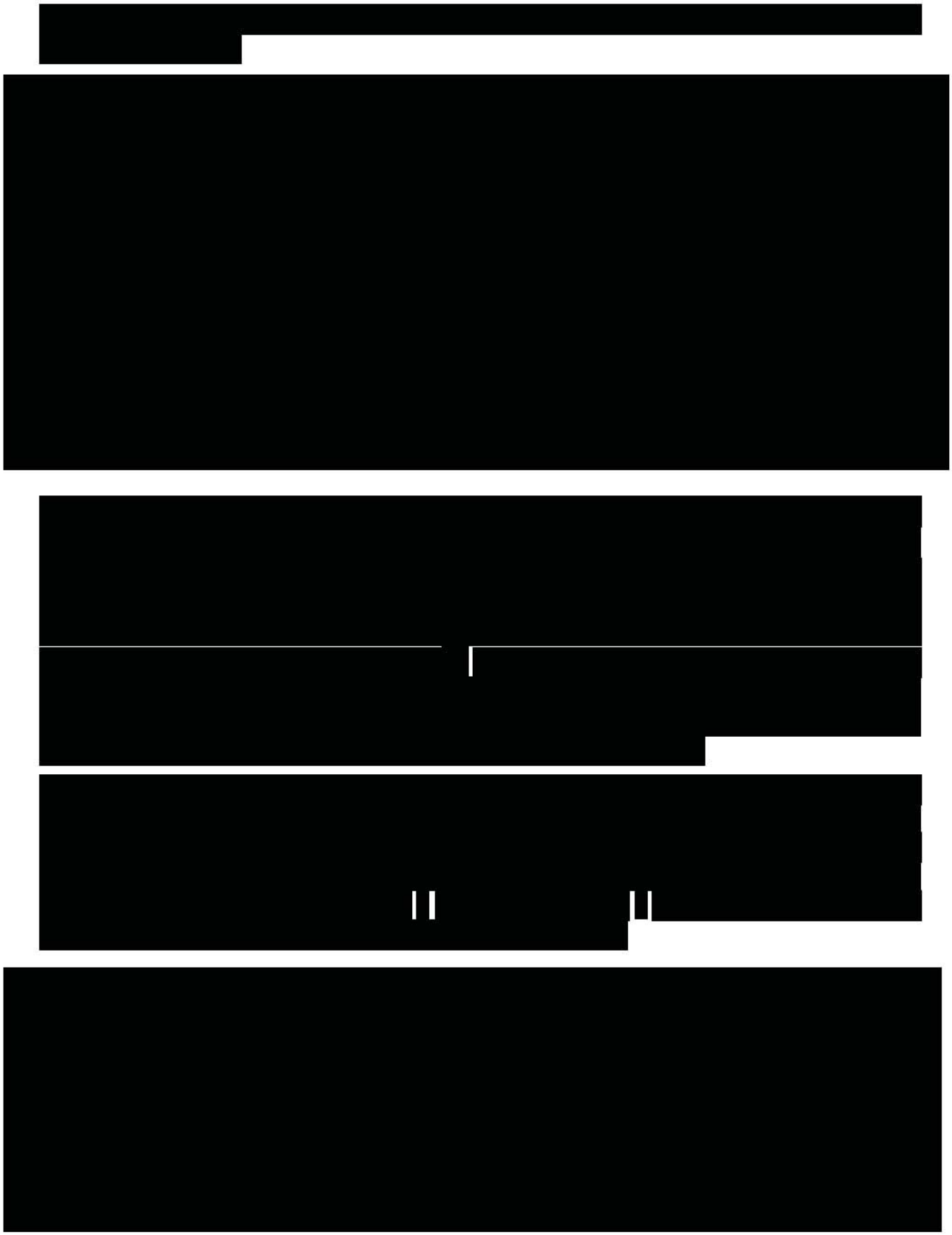
5.3 End of Study Definition

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.

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

[redacted]

[redacted]



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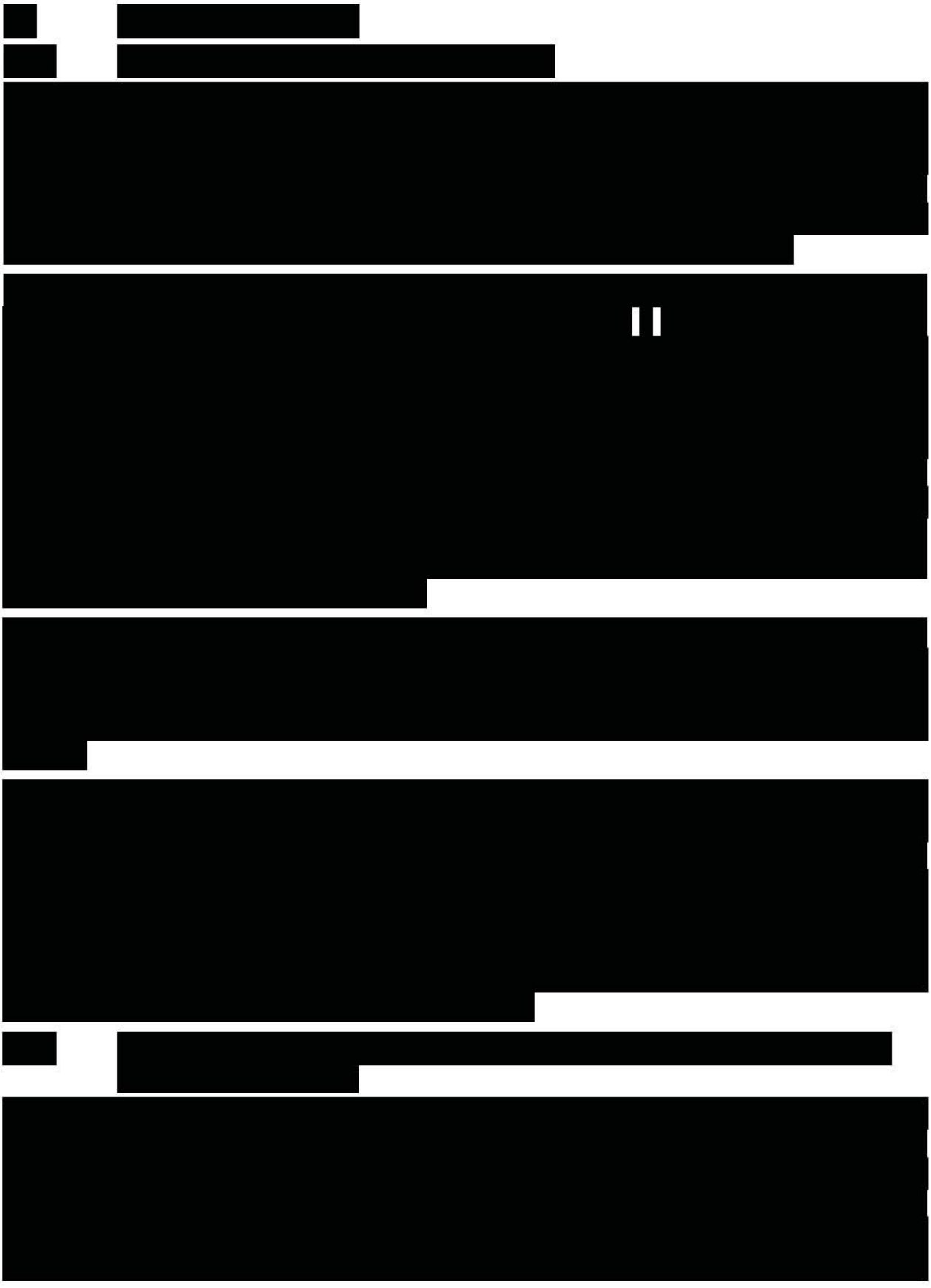

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6 STUDY POPULATION

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 IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) ECOG Performance Status of ≤ 1

b) Participants must have a life expectancy of at least 3 months

c) Histologically confirmed stage IV NSCLC per the 7th International Association for the Study of Lung Cancer classification (IASLC)[43] of squamous or non-squamous histology, with no prior systemic anti-cancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

d) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment. Locally advanced disease with recurrence after chemoradiation therapy (stage IIIB disease, specifically refers to patients with no curative options), is eligible to enroll.

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

f) Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 7); radiographic tumor assessment performed within 28 days before treatment.

g) 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.

h) Participants are to have tumor tissue sample available at a central laboratory for PD-L1 IHC testing during the screening period. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 15 unstained tumor tissue sections, with an associated pathology

report, must be submitted for biomarker evaluation prior to treatment. The tumor tissue sample may be fresh or archival, (archival tissue is to be obtained within 3 months prior to enrollment), and there can have been no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained. Tissue must be from a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

i) Participants must have PD-L1 IHC testing with results performed by a central laboratory during the screening period.

j) Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to treatment. Subjects 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.

k) Screening laboratory values must meet the following criteria (using CTCAE v4):

i) WBC ≥ 2000/ μ L

ii) Neutrophils ≥ 1500/ μ L

iii) Platelets ≥ 100 x 10^3/ μ L

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min 1(using the Cockcroft Gault formula)

Female CrCl = (140 - age in years) x weight in kg x 0.85/ 72 x serum creatinine in mg/dL

Male CrCl = (140 - age in years) x weight in kg x 1.00/ 72 x serum creatinine in mg/dL

vi) AST/ALT ≤ 3.0 x ULN (≤ 5 x ULN if liver metastases are present)

vii) Total bilirubin ≤1.5 x ULN except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL).

Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

a) Males and Females, ages ≥ 18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for methods(s) of contraception for the duration of treatment with nivolumab and 5 months after the last dose of nivolumab (ie 30 days [duration of ovulatory cycle] plus the time required for nivolumab to undergo approximately five half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and up to

7 months after the last dose of nivolumab (ie 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately five half-lives).

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Investigators shall advise WOCBP and male participants who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with known 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 non-squamous histology must have been tested for EGFR mutation status. EGFR test is to be done locally. EGFR test is not provided by a third party laboratory. Use of a FDA-approved test (PCR based assay from tumor tissue) is strongly encouraged. Tests other than PCR or next generation sequencing will be requested to repeat using PCR or next generation sequencing based methods. Participants of non-squamous histology with unknown or indeterminate EGFR status are excluded.

b) Participants with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Participants with unknown or indeterminate ALK status may be enrolled.

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

d) Participants with carcinomatous meningitis.

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

f) Participants with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to first treatment and no additional therapy is required or anticipated to be required during the study period.

g) 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.

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

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

j) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites mandated by local requirements.

k) 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.

[redacted]

3) Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

b) Participants with ≥ Grade 2 peripheral neuropathy

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

5) Other Exclusion Criteria

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

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

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.

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 are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening Period

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

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

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

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo 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:

In this protocol, investigational product(s) is/are:

- Nivolumab
- Ipilimumab
- Carboplatin
- Pemetrexed
- Paclitaxel
- Cisplatin

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-investigational products.

Table 7-1: Study treatments for CA2099LA

Product Description and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Primary Packaging (Volume)/Label Type and Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open label	10 mL per vial and 5 or 10 vials per carton	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5mg/mL)	IP	Open label	40 mL vial and 4 vials per carton	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Carboplatin Solution for Injection[b]	450 mg/vial (10 mg/mL)	IP	Open label	45 mL per vial and 4 vials per carton/	Clear, colorless or slightly yellow solution	Product should be stored as per market product conditions
Paclitaxel Solution for Injection[b]	100 mg/vial (6 mg/mL)	IP	Open label	16.7 mL vial and 4 vials per carton	Clear, colorless, or slightly yellow viscous solution	Product should be stored as per market product conditions
Pemetrexed Powder for Concentrate for Solution for Infusion[b]	500 mg/vial	IP	Open label	500 mg per vial and 1 vial per carton	White to either light yellow or green-yellow lyophilized powder	Product should be stored as per market product conditions
Cisplatin Solution for Infusion[b]	100 mg/vial (1 mg/mL)	IP	Open label	100 mL per vial and 4 vials per carton	Clear, colorless solution	Product should be stored as per market product conditions

NOTES:

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

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

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Treatments Administered

	Week 1, Cycle 1 Day 1 ± 3 Days	**Week 4, Cycle 2 Day 1 ± 3 days**	**Week 7, Cycle 3 Day 1 ± 3 Days**
Nivolumab + ipilimumab + platinum-doublet chemotherapy q 3wk x 2 cycles followed by nivolumab (360 mg q 3weeks) + ipilimumab (1mg/kg q 6weeks)	Cycle 1 Nivolumab + Ipilimumab + Histology-based chemotherapy	Cycle 2 Nivolumab + Histology-based chemotherapy	Cycle 3 Nivolumab + Ipilimumab
Platinum doublet chemotherapy q 3wk x 4 followed by optional maintenance Pemetrexed for non-squamous histology	Cycle 1 Histology-based chemotherapy	Cycle 2 Histology-based chemotherapy	Cycle 3 Histology-based chemotherapy

Both nivolumab and ipilimumab should be administered as 30 minute infusions. Nivolumab will be administered first. Ipilimumab will be administered after at least 30 minutes after completion of the nivolumab infusion. Platinum-doublet will start at least 30 minutes after completion of the nivolumab or ipilimumab infusion (if ipilimumab is scheduled to be given). At the investigator's discretion, nivolumab or ipilimumab may be administered over a longer infusion time (60 minutes) if the participant developed a prior infusion reaction.

Nivolumab and ipilimumab treatment will continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure. Participants will be treated up to 24 months in the absence of disease progression or inacceptable toxicity. Treatment with nivolumab and ipilimumab could be reinitiated as per the initial schedule for subsequent disease progression after maximum 24 months of treatment and administered for up to 1 additional year. Maximum 24 months of treatment also applies to treatment beyond progression.

All participants will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 7.4.1, 7.4.2, 7.4.3, and 8.1.

7.1.1 Dosing

7.1.1.1 Nivolumab and Ipilimumab Dosing for Treatment Arm

Participants will receive nivolumab and ipilimumab (induction dose and treatment interval will be determined by safety lead-in phase in study CA209568), followed by chemotherapy on day 1 of every 3 weeks cycle. The 2 cycles of chemotherapy during induction are same regimens as control arm (without chemotherapy maintenance) as in Section 7.1.1.2. At the time of completion of 2 cycles of chemotherapy, participants who have not experienced disease progression will continue to receive nivolumab at a dose of 360 mg as 30 minute infusion every 3 weeks, and ipilimumab 1 mg/kg as 30 minute infusion IV every 6 weeks starting on day 1. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Treatment with nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity. A maximum 24 months of treatment also applies to treatment beyond progression. Treatment with nivolumab and ipilimumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year (investigators may decide not to re-treat with ipilimumab and nivolumab at progression if there is significant risk of recurrent severe toxicity). Ipilimumab and/or nivolumab must not be reinitiated if it was permanently discontinued on study due to treatment related toxicities. All exceptions must require approval by Medical Monitor. Participants may discontinue only ipilimumab and continue treatment with nivolumab if certain circumstances are met (Section 8.1.2).

Ipilimumab is not permitted to continue on study after nivolumab is discontinued. The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued. The assessment for discontinuation of nivolumab/ipilimumab should be made separately from chemotherapy. If criteria for discontinuation for nivolumab and ipilimumab are met, platinum doublet chemotherapy may continue until 2 cycles have been completed. If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to all or any one study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

7.1.1.2 Chemotherapy Dosing

In control arm, 4 cycles of histology-based platinum doublet chemotherapy options will be selected by investigator and administered on day 1 every 3 weeks; participants with non-squamous 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 8.1.3).

In treatment arm, 2 cycles of chemotherapy during induction are same regimens as control arm (without chemotherapy maintenance).

Histology-based chemotherapy:

- Squamous histology: carboplatin AUC 6 + paclitaxel 200 mg/m^2
- Non-squamous histology:
  - carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2
  - cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

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

Note: The investigator must decide prior to randomization whether or not a participant with non-squamous histology will receive cisplatin, if eligible.

7.1.1.2.1 Paclitaxel and Carboplatin

Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC 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 standard.

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 x ([CrCl (ml/min) + 25]
- Creatinine clearance (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

Oral 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 intravenous (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.

7.1.1.2.2 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% weight used to calculate the previous dose.

Premedications with pemetrexed use

1) Oral corticosteroid 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. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately one 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 non-squamous histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed)
2) 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 75mg/m^2 infusion as per local standard practice on day 1 of a 3-week treatment cycle for up to 2 cycles in treatment arm or 4 cycles in control arm.

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 the following sections for more details: Section 7.4.1 (dose delays);, Section 7.4.2 (dose reductions); Section 7.4.3 (retreatment), and Section 8.1 (dose discontinuations).

All participants who will be receiving 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 platinum doublet cycles (up to 2 cycles in treatment arm or 4 cycles in control arm in total). Dosing for pemetrexed/carboplatin for such participants should follow the instructions in the pemetrexed/carboplatin with or without Pemetrexed Continuation Maintenance section below.

7.1.1.2.3 Pemetrexed/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% weight used to calculate the previous dose.

Oral 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. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately one 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 non-squamous 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 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 x (CrCl [ml/min] + 25)
- Creatinine clearance (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 guideline and regulation. The dose of chemotherapy may be capped per local standards.

7.1.1.3 Optional Continuation-Maintenance

After cycle 4 in control arm, participants with non-squamous histology who have stable disease or response after induction chemotherapy are permitted to receive pemetrexed 500 mg/m² alone as maintenance therapy until disease progression or unacceptable toxicity.

7.1.2 Treatment of Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin 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 NCI CTCAE (Version 4.0) 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 nivolumab or ipilimumab administrations.

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

- Stop the nivolumab or ipilimumab 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 nivolumab or ipilimumab 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 electronic case report form (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 nivolumab or ipilimumab 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 nivolumab or ipilimumab. 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. Nivolumab or ipilimumab 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).

7.1.3 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[21]

Participants will be permitted to continue on nivolumab + ipilimumab for treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Participant is tolerating 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 nivolumab and ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. A follow-up scan should be performed within six (6) weeks ± 7 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed per protocol defined schedule ± 7 days until further progression is determined.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule in Section 2.

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden 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. Nivolumab and ipilimumab 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.

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 by calling an interactive web response system (IWRS) to obtain the participant number. Every participant that signs the informed consent form must be assigned a participant number in IWRS. Specific instructions for using IWRS 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
- Participant number
- Date of birth

Participants enrolled will be grouped according to PD-L1 status (positive, negative, or not quantifiable, using membranous staining in ≥ 1% tumor cells vs membranous staining in < 1% tumor cells). PD-L1 expression data will be transferred directly from analyzing lab to IWRS. IWRS will be used to track the enrollment number.

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

- Participant number
- Date of birth
- Gender
- Histology (squamous or non-squamous).
  - Participants with mixed histology should be classified according to the predominant histology.
  - Participants with adenosquamous histology should be classified as non-squamous histology.
- PD-L1 status
- Will participant be treated with cisplatin, if eligible?

Participants meeting all eligibility criteria will be stratified by tumor histology (squamous vs non-squamous), gender (male vs female), and PD-L1 level (< 1% vs ≥ 1% expression levels) Participants will be randomized in a 1:1 ratio to treatment and control arms.

Note: participants whose PD-L1 status is not quantifiable will be classified as PD-L1 < 1%. The total number of participants with not quantifiable PD-L1 status should not exceed 10% of total randomized participants for Part 2.

Enrollment will end after approximately 420 participants are randomized.

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

7.3 Blinding

Not applicable. This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in Appendix 6.

7.4.1 Dose Delay Criteria

7.4.1.1 Dose Delay Criteria for Nivolumab and Ipilimumab

Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and 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 total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require a dose delay
  - If a participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

Participants who require delay should be re-evaluated weekly or more frequently if clinically indicated. Participants should resume dosing when re-treatment criteria are met.

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5 day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.
- Treatment arm: if any adverse event meeting the dose delay criteria for chemotherapy is felt to be related to only one particular agent in the platinum doublet chemotherapy regimen, then that chemotherapy agent alone may be omitted for that cycle while the other agents (nivolumab and one themotherapy agent) are given. Dosing of nivolumab and both chemotherapy agents should be delayed if any criteria for nivolumab or "both platinum-doublet chemotherapy agents" are met.

7.4.1.2 Dose Delay Criteria for Chemotherapy

Chemotherapy drugs should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1500/μL
- Platelets < 100,000/mm3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event

- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
- Grade 3 lymphopenia does not require dose delay.
- If a participant has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, 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.
- Participants receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft 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 cycles when the participant meets retreatment criteria. Note that pemetrexed can only be administered if CrCl is ≥ 45 ml/min (calculated per Cockroft-Gault formula)
- In addition, if participants receiving carboplatin with paclitaxel and must discontinue carboplatin, the paclitaxel may be continued at the investigator's discretion.
- If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only one particular agent in the platinum doublet chemotherapy 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 7.4.2.2 to determine if dose reduction of the resumed agent is required.
- If both drugs in the platinum doublet chemotherapy 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 7.4.3.3).
- Treatment arm: Dosing of nivolumab and both chemotherapy agents should be delayed if any criteria for nivolumab or "both platinum-doublet chemotherapy agents" are met.

7.4.2 Dose Reductions

7.4.2.1 Dose Reduction for Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

7.4.2.2 Dose Reduction for Chemotherapy

Dose reductions of chemotherapy may be required, and will be performed according to Table 7.4.2.2-1. 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 platinum doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.2.2-1: Dose Modifications of Chemotherapeutic Agents

Dose Level	Carboplatin	Pemetrexed	Paclitaxel	Cisplatin
Starting dose	AUC 6 or AUC 5	500 mg/m²	200 mg/m²	75 mg/m²
First dose reduction	AUC 5 (if starting dose is AUC 6) or AUC 4 (if starting dose is AUC of 5)	375 mg/m²	150 mg/m²	56 mg/m²
Second dose reduction	AUC 4 (if starting dose is AUC 6) or AUC 3 (if starting dose is AUC 5)	250 mg/m²	100 mg/m²	38 mg/m²
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue

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

7.4.2.3 Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 7.4.2.3-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for platinum doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the platinum doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 7.4.2.3-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

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

7.4.2.4 Chemotherapy - Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described in Section 7.4.2.2. 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 two drugs in the platinum-doublet chemotherapy regimen are not linked and may be reduced independently, as summarized in Table 7.4.2.4-1.

Table 7.4.2.4-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Paclitaxel	Carboplatin	Pemetrexed	Cisplatin
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	No change	Reduce one dose level	No change
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce one dose level	No change	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	No change	Discontinue if creatinine clearance < 20 ml/min	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

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

7.4.3 Criteria to Resume Dosing

7.4.3.1 Criteria to Resume Nivolumab Dosing

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.

- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 8.1.
- Participants who delay study treatment due to any Grade 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, which is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.

7.4.3.2 Criteria to Resume Ipilimumab Dosing

Participants may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.
- Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab dose.

- In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- NOTE: One exception occurs when ipilimumab and nivolumab doses are delayed due to drug-related Grade 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade 3 amylase or lipase abnormality is related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only resume when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The BMS Medical Monitor should be consulted prior to resuming ipilimumab in the participant.

7.4.3.3 Criteria to Resume Treatment with Chemotherapy

- Participants may resume treatment with chemotherapy when the ANC returns to 1500/µl. l, the platelet count returns to 100,000/mm^3, 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 7.4.2.2.

7.5 Preparation/Handling/Storage/Accountability

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy manual for complete storage, handling, dispensing, and infusion information.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study Participants. The investigational product 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.

Investigational product 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 treatment are provided in Appendix 2 and Study Reference Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

[redacted]

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 first treatment 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 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 bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment.

7.7.2.2 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 1.1. 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 1.1, 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 1.1 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 7.1.3) in order to resume immunotherapy after palliative local therapy. If radiographic progression per RECIST 1.1 is identified prior to the initiation of palliative local therapy, sites must request a BICR from the third party radiology vendor (Section 5.1.1.2). 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 nivolumab/ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab/ipilimumab 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 nivolumab or nivolumab plus ipilimumab.

7.7.2.3 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and

contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

7.8 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 the nivolumab or ipilimumab 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

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 case report form. Tumor assessments for participants who discontinue study treatment without radiographic progression, confirmed by BICR (Section 5.1.1.2), should continue as per protocol until radiographic progression is determined by blinded independent central review.

If participant is intolerant of nivolumab treatment during the chemotherapy cycles, participant should be withdrawn from the treatment phase of the study.

Chemotherapy dose reduction is allowed on study. Any participant with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A participant in treatment arm who is discontinued from the chemotherapy treatment will remain on the study and receive nivolumab and ipilimumab therapy with option of pemetrexed maintenance (non-squamous histology only).

If the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the participant meets criteria to resume nivolumab treatment.

8.1.1 Nivolumab Dose Discontinuation

Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm);
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration;
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
- Any drug related liver function test (LFT) abnormality that meets the following criteria require discontinuation
  - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*

    * In most cases of Grade 3 AST or ALT elevation, study drugs(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drugs(s), a discussion between the investigator and the BMS medical monitor or designee must occur.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
  - Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- ♦ Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

– Dosing delays lasting > 6 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. 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.

– Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen), the participant should discontinue all treatment: nivolumab, ipilimumab and chemotherapy (if chemotherapy is part of the treatment regimen), and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been completed.

8.1.2 Ipilimumab Dose Discontinuation

Ipilimumab should be permanently discontinued if any of the following criteria are met:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - Grade ≥ 3 drug related AST, ALT or Total Bilirubin required discontinuation

  - ♦ * In most cases of Grade 3 AST, ALT evaluation study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS medical monitor or designee must occur.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2X ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks 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 > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued ipilimumab dosing

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen), the participant should discontinue nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen) and be taken off the treatment phase of the study. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for

discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been completed.

8.1.3 Chemotherapy Dose Discontinuation

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

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10x ULN for > 2 weeks
  - AST or ALT > 10x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event 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 adverse event 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 that drug(s) with the following exception:
  - Dosing delays lasting > 6 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued platinum doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.
- For participants in control arm 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 3 cycles of chemotherapy. The nature and grade of the toxicity must be clearly noted, and the medical monitor must be notified.

- In addition, participants receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated creatinine clearance 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 remainder of the platinum doublet cycles when the participant meets retreatment criteria.

Note: For participants in treatment arm, if the investigator is unable to determine whether an adverse event is due to nivolumab or ipilimumab or platinum doublet chemotherapy, then all drugs must be discontinued. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 2 cycles have been completed.

A participant in treatment arm who is discontinued from the chemotherapy treatment due to toxicities related to chemotherapy only, will remain on the study and receive nivolumab and ipilimumab therapy.

8.2 Discontinuation from Study

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

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

8.2.1 Post Study Treatment Study Follow-up

In this study, OS is a key endpoint of the study. 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 for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

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.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities in Section 2.

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099LA Imaging Charter to be provided by the core lab.

9.1.1 Methods of Measurements

The following imaging assessments should be performed at pre-specified intervals: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease.

- Baseline assessment must occur prior to dosing
- CT scans should be acquired with slice thickness of 5 mm or less with no intervening gap (continuous)
- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other sites of disease may be obtained. MRIs should be acquired with slice thickness of 5 mm or less with no gap (continuous).
- Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.

NOTE: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with FDG-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. If a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the scan introduces additional data which may bias an investigator if it is not routinely or serially performed.

MRI of brain is required at screening in order to rule out active metastatic disease.

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

9.1.2 Imaging and Clinical Assessment

Screening baseline tumor assessments must be performed within 28 days prior to randomization. In addition to the chest, abdomen, pelvis, and brain (to rule out brain metastases), all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease using the same imaging method and technique as was used at baseline.

Radiographic tumor response will be assessed at week 6 (± 7 days) from first dose date, then every 6 weeks (± 7 days) for the first 12 months (until Week 48) and every 12 weeks (± 7 days) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Participants with a history of brain metastasis may have surveillance MRI approximately every 12 weeks (± 7 days) from the date of first dose, or sooner if clinically indicated.

Tumor assessments for each participant should be submitted to the radiology vendor, as they are performed on an ongoing basis. The blinded, independent radiologists will review all available tumor assessments for that given participant and determine if RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given participant met RECIST 1.1 criteria for progression will be provided to the site. Participants whose disease progression is not confirmed centrally will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule.

The BICR will also review tumor images in all treated participants to determine RECIST 1.1 response for the analyses of ORR and PFS. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

9.1.2.1 Assessment of Baseline Tumor Assessment

Screening/baseline imaging (ie, CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease) should be submitted to the imaging core lab. MRI preferred or CT scan of the brain should be performed within 28 days of randomization and submitted to the imaging core lab.

9.1.2.2 BICR Assessment of Progression

Sites should submit all scans to BICR on a rolling basis, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans on a rolling basis and remain blinded to treatment arm and investigator assessment of submitted scans. When progression is diagnosed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be performed.

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 until the BICR confirms progression on a subsequent tumor assessment. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2, until progression has been confirmed by BICR.

9.1.3 Study Outcomes Research Assessments

The evaluation of health related quality of life is an increasingly important aspect of a clinical efficacy. Such data provides an understanding of the impact of treatment from the participants' perspective and offers insights into the patient experience that may not be captured through physician reporting. Generic health related quality of life scales additionally provide data necessary in calculating utility values for health economic models. In this study, the EQ-5D (EQ-5D-3L) will be collected in order to assess the impact of study treatment on generic health related quality of life, which will also be used in populating health economic models most notably, cost effectiveness analysis. The Lung Cancer Symptom Scale (LCSS) will be collected to assess the impact of study treatment on patient reported disease-related symptoms.

The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D includes a 5-dimension descriptive system as well as a visual analog rating scale (VAS). The EQ-5D descriptive system is comprised of the following 5-dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Utility data generated from the EQ-5D 3L are recommended for use in cost effectiveness analysis. The EQ-5D VAS records the participant's self-rated health status on a 100-point vertical visual analogue scale (0=worst imaginable health state, 100 = best imaginable health state).

The LCSS is a validated instrument designed to assess the impact of treatment on disease-related symptoms. It consists of 6 symptom-specific questions related to dyspnea, cough, fatigue, pain, hemoptysis and anorexia plus 3 summary items: symptom distress, interference with activity, and global health related quality of life (HRQoL). The questionnaire uses a 24-hour recall period. For the six individual symptom measures, the degree of impairment is recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score. The LCSS average symptom burden index (ASBI) can be derived as the average of scores for the six symptom-related items. A clinically meaningful change in ASBI score has been defined as 10 points.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and within 100 days of discontinuation of dosing at the timepoints specified in the Schedule of Activities (Section 2).

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period (after signing the consent) and within 100 days of discontinuation of dosing. For participants randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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.

- 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 section.
- 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 within 24 hours of this being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

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

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

Section 9.2.6 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A 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 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the particpant.

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

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

9.2.6 Adverse Events of Special Interest

Definition of Immune-mediated Adverse Events (IMAEs)

Immune-mediated AEs 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 100 days of the last dose. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 9.2.6-1 below provides a summary of the IMAEs category and their respective preferred terms. This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 9.2.6-1: 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	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
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

9.2.7 Laboratory Test Result Abnormalities

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

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

- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.8 Potential Drug Induced Liver Injury (DILI)

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).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

9.2.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, 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

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).

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 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

Hematology (CBC)	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Glucose Albumin	Sodium Potassium Chloride Calcium, Corrected calcium Phosphorus Magnesium Amylase Lipase
Serology	
Serum for hepatitis C antibody or HCV RNA, hepatitis B surface antigen (screening only) HIV testing (if mandated locally)	
Other Analyses	
TSH with reflexive fT3 and fT4 if TSH is abnormal	
Pregnancy test (WOCBP only: screening and during study)	

9.4.4 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.

9.4.5 Electrocardiogram (ECG)

All subjects who have met the eligibility criteria are required to have a 12-lead ECG performed during Screening. If clinically indicated, additional ECGs may be obtained during the study

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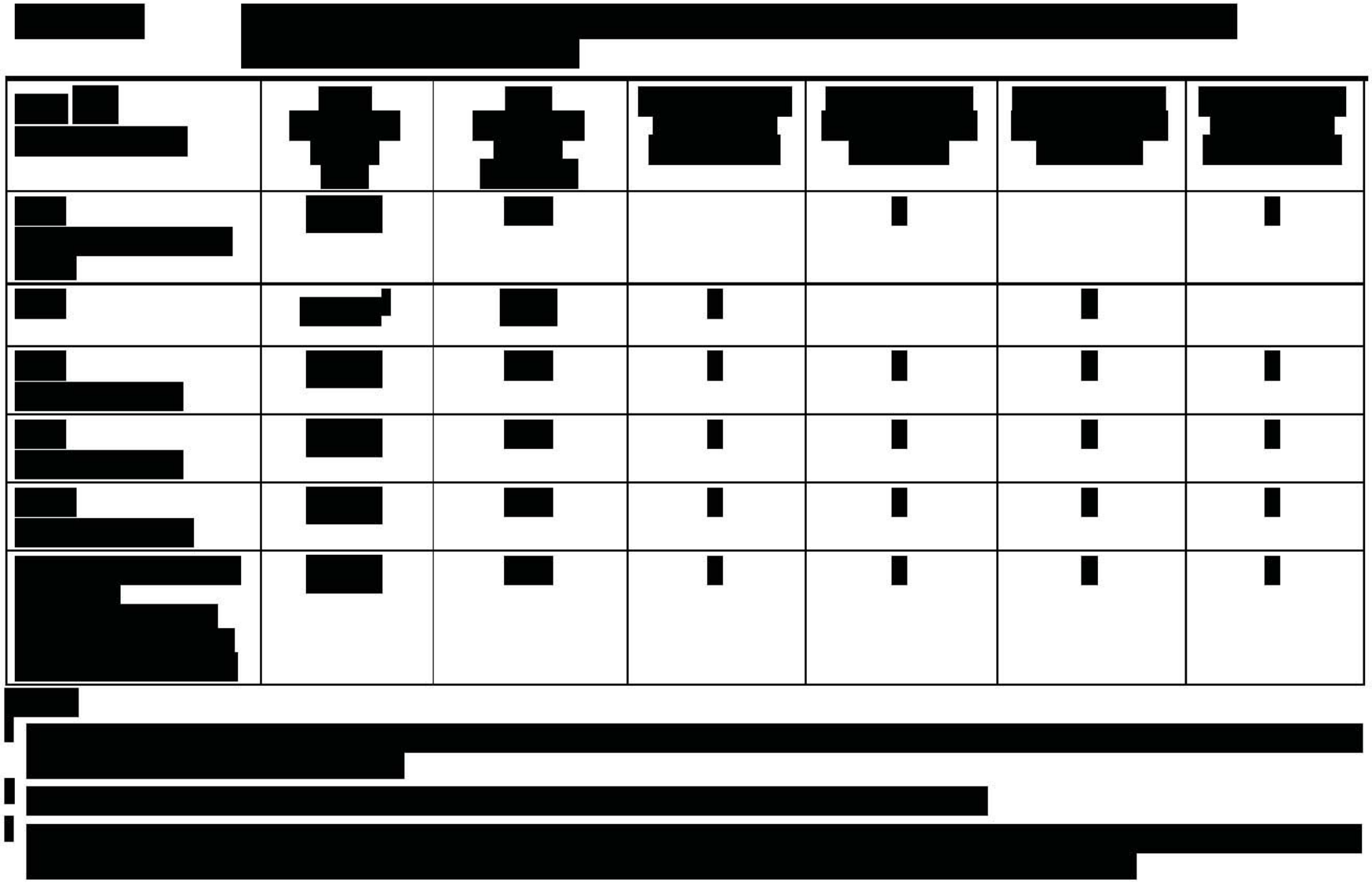

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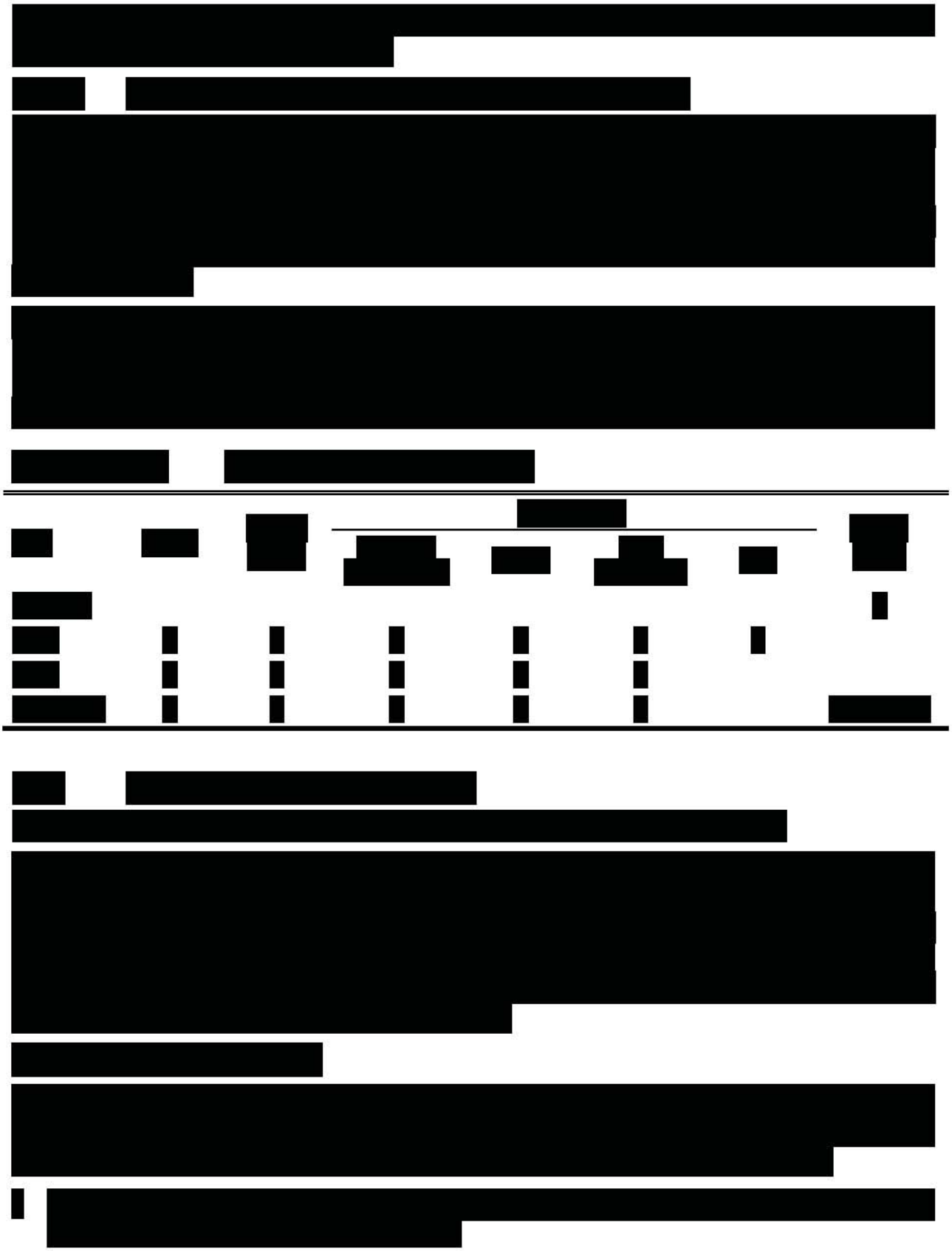

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10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size is based on the comparison of the primary endpoint of OS between nivolumab and ipilimumab plus chemotherapy and chemotherapy alone, with two-sided overall alpha of 0.05. The number of events was estimated assuming an exponential distribution of OS in each arm.

Approximately 420 participants will be randomized to treatment arm and control arm in a 1:1 ratio. Approximately 233 events (ie, deaths), observed among the 420 randomized participants, provides 90% power to detect a hazard ratio (HR) of 0.65 with a type 1 error of 0.05 (two-sided). The HR of 0.65 corresponds to a 54% increase in the median OS, assuming a median OS of 13.3 months for chemotherapy alone and 20.5 months for nivolumab and ipilimumab plus chemotherapy respectively. There are two planned interim analysis of OS for superiority at approximately 70% and 85% of total events, ie, 163 and 198 deaths. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. It is estimated that it will take approximately 18/21/25 months from the randomization of the first participant to observe the required number of events for the two interim and the final OS analysis, with approximately 11 months of accrual to reach 420 randomized participants, assuming a piecewise accrual rate (20 for the first month, and 40/month starting from the second month).

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and were registered into the IWRS
Randomized	All participants who were randomized to either treatment arm. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, and outcome research.
Treated	All participants who received at least one dose of any study medication. This is the primary dataset for dosing and safety analysis.

The efficacy analysis for secondary endpoints will be performed by treatment group as randomized for all randomized participants.

10.3 Statistical Analyses

The statistical analysis plan 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.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Primary endpoint is OS with nivolumab and ipilimumab plus chemotherapy vs. chemotherapy alone. OS is defined as the time between the date of the randomization date and the date of death due to any cause. OS will be censored on the last date a participant was known to be alive.
Secondary	• BICR assessed PFS with nivolumab and ipilimumab plus chemotherapy vs. chemotherapy alone • BICR ORR with nivolumab and ipilimumab plus chemotherapy vs. chemotherapy alone • ORR, PFS, and OS in nivolumab and ipilimumab plus chemotherapy vs. chemotherapy in subgroups with different PD-L1 expression levels • Tumor cell total somatic mutations and their association with ORR, PFS, and OS PFS is defined as the time from the randomization date to the date of the first documented tumor progression as determined by the BICR (per RECIST 1.1), or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments will be censored on the randomization date. Participants

Endpoint	Statistical Analysis Methods
	who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first. ORR is defined as the number of participants with a best overall response (BOR) of confirmed CR or PR divided by the number of treated participants. BOR is defined as the best response designation, as determined by the BICR, recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anti-cancer therapy, whichever occurs first. For participants without documented progression or palliative local therapy or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For participants who continue treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. Further characterization of the response will include time to OR (time from first dosing date to first CR or PR) and depth of response (maximum tumor shrinkage in target lesions).

10.3.1.1 Methods for Primary Endpoints

The efficacy analysis will be performed by treatment group as randomized. For the primary endpoint, the distribution of OS will be compared in two randomized arms at the two interim and final analysis via a two-sided, log-rank test stratified by PD-L1, histology and gender with an overall significance level of 0.05. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses. Hazard ratios and corresponding two-sided 95% confidence intervals (CI) will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by above factors. OS curves OS medians with 95% CIs, and OS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirement is met.

10.3.1.2 Methods for Secondary Endpoints

The efficacy analysis for secondary endpoints will be performed by treatment group as randomized for all randomized participants. PFS comparison will be conducted. The comparison will be based on a two-sided stratified log-rank test, stratified by PD-L1, histology and gender at a two-sided alpha of 0.05 level. Hazard ratios and corresponding two-sided 95% confidence intervals (CI) will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 18, 24, 36, and 48 months with 95% CIs will be estimated using Kaplan-Meier methodology if follow-up requirement is met.

The comparison of ORR as per BICR assessment will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1, histology and gender to compare the treatment group to the control group. An estimate of the difference in ORRs and their corresponding 95% exact CI will also be calculated. The number and percentage of participants in each category of best overall response per BICR (confirmed complete response [CR], confirmed partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UD]) according to the BICR will be presented, by treatment group. An estimate of the response rate and an associated exact two-sided 95% CI (Clopper and Pearson) will be presented, by treatment group.

ORR, PFS and OS will also be assessed by treatment groups within subgroups of PD-L1 expression levels: PD-L1 positive, PD-L1 negative, PD-L1 not quantifiable. The pre-specified TMB thresholds will be used to categorize participants in subgroups. ORR, PFS and OS will be assess by TMB subgroups.

10.3.2 Safety Analyses

Safety analysis will be performed in all treated participants. Analysis on randomization phase will be based on treatment groups. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug related AEs, SAEs and drug-related SAEs, AEs and drug-related AEs leading to drug discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term, based on MedDRA terminology. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

A tabular summary of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. Frequency, management and resolution of IMAEs will be analyzed and a descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE will be individually characterized by IMAE category (see Section 9.2.6).

Endpoint	Statistical Analysis Methods
Exploratory	Safety and tolerability objectives will be measured by the incidence of adverse events, serious events, deaths, and laboratory abnormalities.

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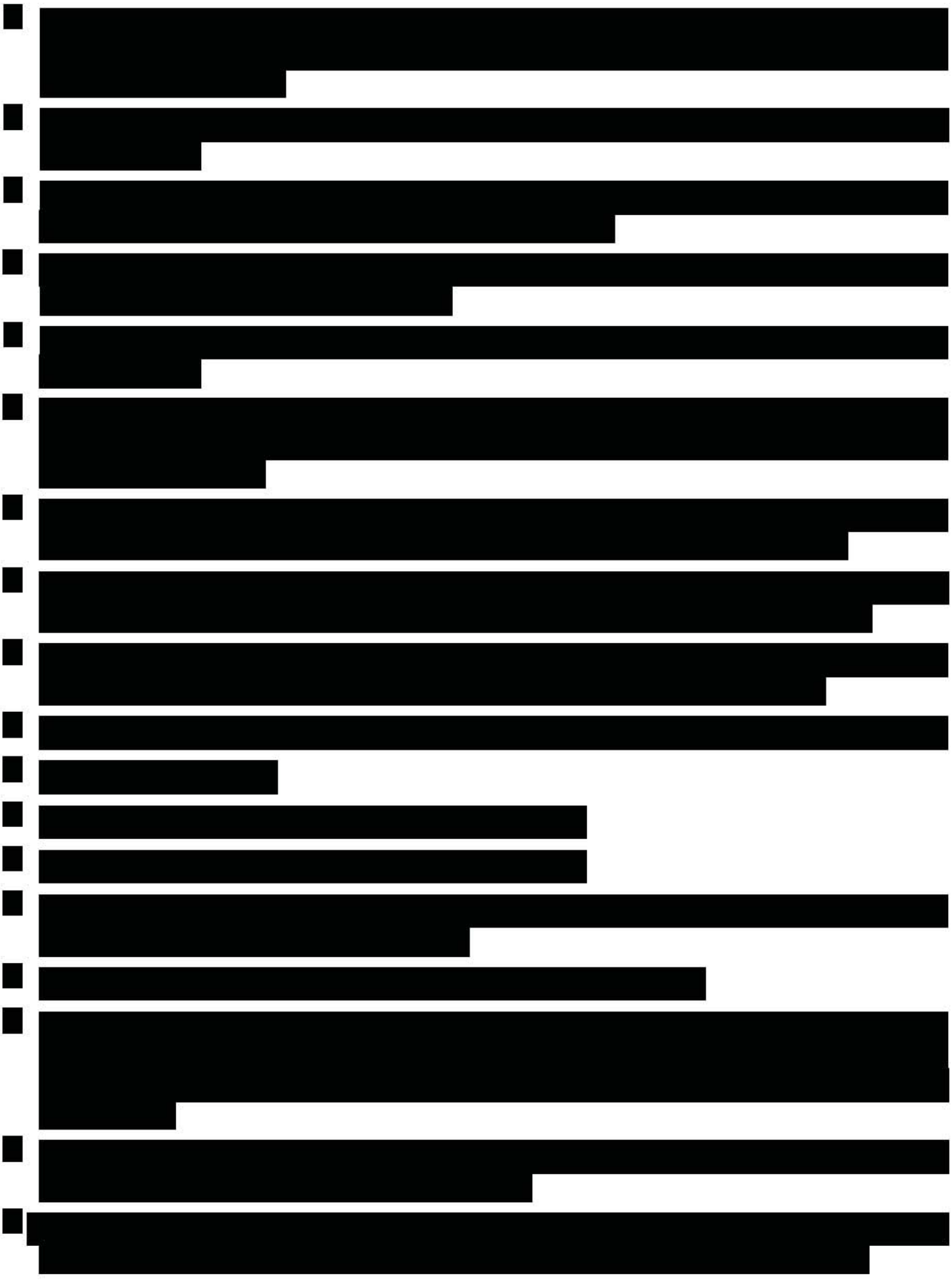
10.3.6 Interim Analyses

Two formal interim analysis for the OS are planned after 163 and 198 deaths have been observed respectively, which are expected to occur approximately 18 and 21 months after study initiation. At the time of the interim analysis, the DMC will review efficacy and safety data as specified in the DMC charter. This formal comparison of OS will allow for early stopping for superiority. Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. In addition to the formal planned interim analyses for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. The Statistical Analysis Plan will further describe the planned interim analyses.



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