Official Title of Study:

AA Phase 3, Randomized, Open Label Study to Compare Nivolumab plus Concurrent Chemoradiotherapy (CCRT) followed by Nivolumab plus Ipilimumab or Nivolumab plus CCRT Followed by Nivolumab vs CCRT followed by Durvalumab in Previously Untreated, Locally Advanced Non-small Cell Lung Cancer (LA NSCLC)

NCT Number: NCT04026412

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IND: 125,872
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Date: 26-Apr-2019
Revised Date: 30-Oct-2023

CLINICAL PROTOCOL CA20973L

A Phase 3, Randomized, Open Label Study to Compare Nivolumab plus Concurrent Chemoradiotherapy (CCRT) followed by Nivolumab plus Ipilimumab or Nivolumab plus CCRT Followed by Nivolumab vs CCRT followed by Durvalumab in Previously Untreated, Locally Advanced Non-small Cell Lung Cancer (LA NSCLC)

(CheckMate 73L, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 73L)

Protocol Amendment Number: 03
Incorporates Administrative Letters: 06 and 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	30-Oct-2023	• [redacted] • Introduction of estimands framework per International Council on Harmonisation (ICH) E9 addendum. • Clarifications of language and editorial changes. • Incorporates Administrative Letters 06 and 07. • Replaced text within the CA20973L protocol to comply with EU Clinical Trial Regulation.
Administrative Letter 07	12-Sep-2023	• The purpose of this administrative letter is to advise of a change in study personnel.
Administrative Letter 06	08-Dec-2021	• Corrected error in Section 6.1.1.
Protocol Amendment 02	16-Aug-2021	• Progression-free survival (PFS) statistical assumption and accrual duration updated based on emerging data external to the study. • Added interim analyses of PFS. • Moved overall survival for Arm A vs Arm C from a primary endpoint to a key secondary endpoint. • Number of tumor tissue slides requested at screening reduced from 15 to 5-10. [redacted] • Updated text throughout the document to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collections, treatment administration, and to incorporate country-specific [redacted] feedback. • Incorporates Administrative Letter 03.
Administrative Letter 03	20-Apr-2020	• Clarification to planned chemotherapy regimen. • Clarification to Table 7-1, footnote b.
Revised Protocol 01	04-Mar-2020	• Added carboplatin + paclitaxel as an additional chemotherapy option during CCRT. • Added the option for Cycle 1 of the CCRT Period (systemic anticancer therapy alone) to be skipped if RT planning is complete prior to the start of Cycle 1 therapy. In such cases, participants will initiate treatment with concurrent RT and systemic anticancer therapy (starting at Cycle 2 of the CCRT Period). • Revised PD-L1 stratification to include 3 separate PD-L1 strata: ≥1%, <1%, and indeterminate or not evaluable. In the original protocol, PD-L1 indeterminate or not evaluable participants were included in the <1% subgroup.

Document	Date of Issue	Summary of Change
		• Updated secondary endpoints to include PFS, ORR, CR rate, TTR and DoR per Investigator assessment. • Updated TTDM endpoint to be evaluated per Investigator assessment of images per RECIST 1.1. In the original protocol, TTDM was per BICR assessment of tumor images. • Specified that the planned chemotherapy regimen, the planned number of cycles of chemotherapy (up to 2 cycles or up to 3 cycles), the planned dose level of chemotherapy at the start of treatment for agents with more than 1 possible dose level per protocol (eg, carboplatin, paclitaxel), and the radiation modality must be pre-defined and documented in the IRT and medical records by the investigator prior to randomization. • Clarified that at Screening, a separate contrast enhanced CT of chest, CT or MRI of upper abdomen (including adrenal glands and full liver), and other suspected sites of disease is required if the CT component of the Screening PET/CT is not of sufficient diagnostic quality for RECIST 1.1 assessments. • Clarified that tumor imaging must continue until BICR confirmed disease progression, Investigator-assessed distant metastases, or treatment discontinuation due to additional PD during treatment beyond progression, whichever occurs later. • Added additional clinical background and updates for the NICOLAS and Checkmate 227 trials. • Revised CCRT inclusion criteria 1, 2 and 3; and maintenance inclusion criterion 5. • Revised CCRT exclusion criteria 1, 2 and 5; and maintenance exclusion criterion 7. • Added additional instructions for CCRT and imaging. • [redacted] • Incorporated requests from local [redacted] reviews of original protocol. Updated document with Administrative Letter 01 and 02 changes.
Administrative Letter 02	14-Jan-2020	• Clarified the intent of CCRT Exclusion criteria 2f.
Administrative Letter 01	27-Jun-2019	• Clarified that legal authorized representative (LAR) will be allowed. • To allow EGFR test performed by central lab. • [redacted] • Corrected typographic errors for the protocol consistency. • To correct spelling errors in the protocol.
Original Protocol	26-Apr-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

[redacted]

Protocol revisions are specified below and have also been incorporated into the Protocol Summary (Synopsis). Approved administrative letter changes have also been incorporated in this protocol amendment, but not noted in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Title Page	• EudraCT number replaced by European Union (EU) trial number. • Clinical Trial Physician contact personnel updated.	• Applied the new administrative reference to comply with EU Clinical Trial Regulation (EU CTR), following the transition to EU CTR. • Change in personnel.
Table 2-1: Screening Procedural Outline - All Study Arms (Arm A, Arm B, and Arm C) for CA20973L	• Updated "within 28 days of" to "within 28 days prior to" for brain imaging assessment notes.	• To clarify brain imaging should be performed 28 days prior to randomization and does not include the day of randomization.
Section 4.1: Estimand for Primary Objective Table 4.1-1: Summary of Attributes of the Main Estimand for Primary Objective Table 4.1-2: Summary of Attributes of the Supplemental Estimand for Primary Objective Section 4.2: Estimand for Key Secondary Objective Table 4.2-1: Summary of Attributes of the Main Estimand for Secondary Objective (Arm A vs Arm C) Table 4.2-2: Summary of Attributes of the Main Estimand for Secondary Objective (Arm B vs Arm C)	• Added new sections and tables.	• To define the methods of comparing population treatment effect outcomes in the same participants under different treatment conditions as required per International Council on Harmonisation (ICH) E9 addendum.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1.1: Inclusion Criteria for CCRT	• Updated "legal acceptable representatives (LAR)" to "legally acceptable representatives (LAR)."	• Additional language was added to align with current Bristol-Myers Squibb Company (BMS) protocol model document (PMD).
Section 7.7.2: Prior and Concomitant Medications	• Clarified documentation of medications used for procedures (eg, biopsy) is encouraged.	• To clarify medications used for procedures are encouraged but not required to be reported.
Section 7.8: Treatment After the End of the Study	• Additional text regarding rights for which the study treatment could be terminated has been added to align with current BMS PMD.	• To clarify that treatment after end of study will be based on local regulations.
Section 8.3: Lost to Follow-Up	• Additional mandatory text added for section.	• Additional language was added to align with current mandatory language in BMS PMD.
Section 9.2.4: Regulatory Reporting Requirements for SAEs Appendix 2: Study Governance Considerations	• Updated "European Directive 2001/20/EC" to "Regulation EU No. 536/2014" in each respective section.	• To state the new legal framework in the EU after transition to EU CTR.
Section 9.2.5: Pregnancy	• Additional mandatory language regarding pregnancy reporting has been added.	• Additional language was added to align with current BMS PMD.
Section 10.1: Sample Size Determination	• Added language related to the discontinuation of the study within Russia.	• To provide an update on BMS' decision to discontinue the study in Russia and the inclusion of Russian study participants in the primary analysis.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Appendix 2: Study Governance Considerations	• Added 2 new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security.	• Added to align with BMS commitment to diversity in clinical trials and to comply with EU CTR requirements.
Appendix 9: Country-specific Requirements for HIV Testing	• Removed Germany and France specific requirements from Appendix 9.	• EU-specific protocol amendment 01 has already consolidated EU country-specific differences.
Appendix 10: Country-specific Requirements for Imprisonment	• Removed from Appendices.	• EU-specific protocol amendment 01 has already consolidated these country-specific requirements.
All	• Minor typographic and formatting errors.	• Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Open Label Study to Compare Nivolumab plus Concurrent Chemoradiotherapy (CCRT) followed by Nivolumab plus Ipilimumab or Nivolumab plus CCRT Followed by Nivolumab vs CCRT followed by Durvalumab in Previously Untreated, Locally Advanced Non-small Cell Lung Cancer (LA NSCLC)

(CheckMate 73L, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 73L)

Study Phase: 3

Rationale: CA20973L is a phase 3, randomized, open label study to compare nivolumab plus concurrent chemoradiotherapy (CCRT) followed by nivolumab plus ipilimumab or nivolumab alone versus concurrent chemoradiotherapy (CCRT) followed by durvalumab in previously untreated locally advanced non-small cell lung cancer (LA NSCLC).

Adding anti-PD-1 treatment concurrently to CCRT is hypothesized to improve anti-tumor activity. Subsequently, combining immunotherapeutic agents with different mechanisms of action in the maintenance period following CCRT may offer the possibility of a synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Therefore, combining anti-PD-1 and anti-CTLA-4 immunotherapies following CCRT has the potential to improve outcomes.

The current study aims to demonstrate that incorporation of nivolumab to definitive CCRT, followed by nivolumab with/without ipilimumab will be efficacious in participants with newly diagnosed untreated LA NSCLC, compared with CCRT followed by durvalumab. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, [redacted], and changes in patient-reported outcomes for quality of life assessments. The safety and efficacy of ipilimumab added to nivolumab maintenance therapy will be characterized descriptively.

Study Population: Previously untreated locally advanced non-small cell lung cancer (LA NSCLC).

Objectives, Endpoints, and Estimands:

The study objectives and endpoints described below will be evaluated for the following treatment regimens:

- Arm A: Nivolumab + CCRT followed by nivolumab + ipilimumab maintenance
- Arm B: Nivolumab + CCRT followed by nivolumab maintenance
- Arm C: CCRT followed by durvalumab maintenance

Objectives	Endpoints
Primary	
To compare progression-free survival (PFS) for Arm A vs Arm C	• PFS by RECIST 1.1 per BICR
Main Estimand for the Primary Objective: Stratified HR in PFS by RECIST 1.1 per BICR between Arm A and Arm C irrespective of initiation of subsequent anti-cancer therapy	
Secondary	
To compare OS for Arm A vs Arm C	• OS for Arm A vs Arm C
To evaluate PFS and OS for Arm B vs Arm C and Arm A vs Arm B	• PFS by RECIST 1.1 per BICR for Arm B vs Arm C • OS for Arm B vs Arm C • PFS by RECIST 1.1 per BICR for Arm A vs Arm B • OS for Arm A vs Arm B
To evaluate tumor response for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to BICR assessment	• Objective Response Rate (ORR) by RECIST 1.1 per BICR • Duration of response (DoR) by RECIST 1.1 per BICR • Time to response (TTR) by RECIST 1.1 per BICR
To evaluate PFS and tumor response for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to Investigator assessment of tumor imaging	• PFS by RECIST 1.1 per Investigator assessment • ORR by RECIST 1.1 per Investigator assessment • DoR by RECIST 1.1 per Investigator assessment • TTR by RECIST 1.1 per Investigator assessment
To evaluate time to death or distant metastases (TTDM) for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to Investigator assessment of tumor imaging	• TTDM by RECIST 1.1 per Investigator assessment
To assess safety and tolerability of study treatment	• Incidence of AEs, SAEs, and select AEs
To evaluate symptom deterioration for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B	• Proportion of participants without meaningful symptom deterioration following 48 weeks of maintenance therapy based on NSCLC-SAQ
Main Estimand for the Secondary Objective: Stratified HR in OS between Arm A vs Arm C and Arm B vs Arm C	

Abbreviations: AE, adverse event; BICR, blinded independent central review; DoR, duration of response; HR, hazard ratio; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; TTDM, time to death or distant metastases; TTR, time to response.

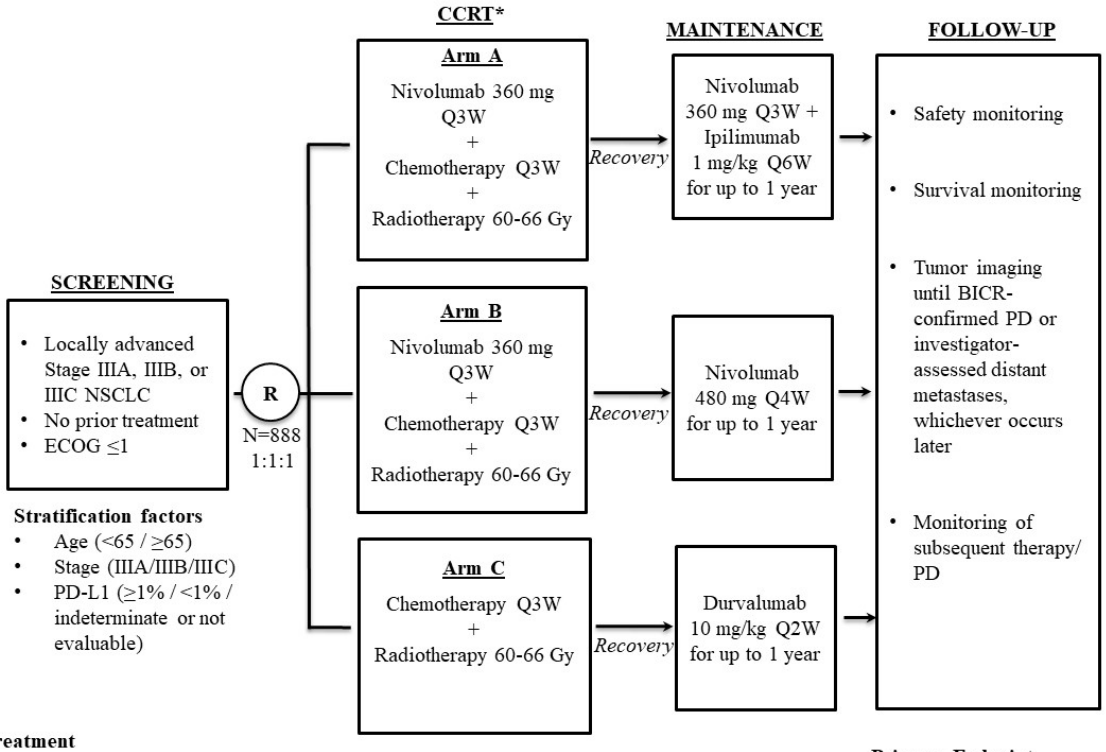
Overall Design: This multicenter, randomized, open label, Phase 3 study compares nivolumab plus CCRT followed by nivolumab and ipilimumab combination (Arm A) or nivolumab plus CCRT followed by nivolumab alone (Arm B) with CCRT followed by durvalumab (Arm C) in

previously untreated LA NSCLC. The safety and efficacy of ipilimumab added to nivolumab maintenance therapy will also be characterized by evaluating Arm A vs Arm B descriptively.

The study is divided into a Screening Period, Concurrent Chemoradiotherapy (CCRT) Period, Recovery Period, Maintenance Period, and a Long-term Follow-up Period. The treatment period will contain a CCRT Period, a Recovery Period, and a Maintenance Period. Randomization will be stratified by:

- Age:
  - < 65 years
  - ≥ 65 years
- Tumor PD-L1 status
  - ≥ 1%
  - < 1%
  - indeterminate or not evaluable
- Stage per AJCC 8th edition:
  - IIIA
  - IIIB
  - IIIC

Study Design Schematic



Treatment

- *CCRT will be up to 3 cycles with 21 days per cycle
  - Systemic anti-cancer therapy (ie, chemotherapy+/- nivolumab) will start at Cycle 1 and RT will start at Cycle 2. If RT planning is complete prior to the initiation of systemic anti-cancer therapy at Cycle 1, Cycle 1 may be skipped and treatment initiated with concurrent RT and systemic anti-cancer therapy (starting at Cycle 2).
- Recovery period will last up to 42 days.
- Maintenance therapy will last up to 12 months.

Primary Endpoint

- PFS by BICR (Arm A vs Arm C)

Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; N, number of participants; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; R, randomize; RT, radiotherapy.

Number of Participants: Assuming approximately a 40% screen failure rate, approximately 1400 participants may be screened to randomize 888 participants with previously untreated locally advanced NSCLC (1:1:1) to the 3 treatment arms.

Treatment Arms and Duration: Participants will be randomized (1:1:1) across the 3 treatment arms:

- **Arm A**:
  - **CCRT Period:** Nivolumab (360 mg flat dose IV Q3W) for cycles 1 to 3 + platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - **Maintenance Period:** Nivolumab (360 mg flat dose IV Q3W) + ipilimumab (1 mg/kg IV Q6W) for up to 12 months

- **Arm B**:
  - **CCRT Period:** Nivolumab (360 mg flat dose IV Q3W) for cycles 1 to 3 + platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - **Maintenance Period:** Nivolumab (480 mg flat dose IV Q4W) for up to 12 months
- **Arm C:**
  - **CCRT Period:** Platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - **Maintenance Period:** Durvalumab (10 mg/kg IV Q2W) for up to 12 months.

If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT Period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT Period are still to be followed. The Recovery Period will begin after the final dose of radiotherapy and the completion of Cycle 3 procedures as outlined in the Schedule of Activities. An additional cycle of consolidation chemotherapy + nivolumab (Arms A and B) or chemotherapy alone (Arm C) will **not** be administered after the completion of radiotherapy in this situation.

Study Drugs for CA20973L		
Medication	**Potency**	**IP/Non-IP**
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP
Ipilimumab Solution for Injection[a]	50 mg (5 mg/mL)	IP
Nivolumab Solution for Injection[b]	100 mg (10 mg/mL)	IP
Cisplatin Solution for Infusion[c]	100 mg/vial (1 mg/mL)	IP
Etoposide Concentrate for Solution for Injection[c]	100 mg/vial (20 mg/mL)	IP
Durvalumab Solution for Injection[c]	500 mg/vial (50 mg/mL)	IP
Carboplatin Solution for Injection[c]	450 mg/vial (10 mg/mL)	IP
Pemetrexed Powder for Concentrate for Solution for Infusion[c]	500 mg/vial	IP
Paclitaxel Solution for Infusion[c]	100 mg/vial (6 mg/mL)	IP

Abbreviations: IP, investigational product; SmPC, Summary of Product Characteristics.

[a] 50 mg ipilimumab vial will be available starting Q3 2022 and may be used in this study.

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

[c] 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. The approved local product label (including package insert, SmPC, or equivalent), or local standards for preparing and administering these agents may be used, as long as there is no change in the treatment dose or administrative schedule, as specified in the protocol.

Data Monitoring Committee: Yes

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline - All Study Arms (Arm A, Arm B, and Arm C) for CA20973L

Procedure	Screening Visit	Notes (28 day window, unless specified otherwise)[a]
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) to obtain participant number at the time informed consent is obtained. Must be obtained prior to performing any protocol-specific screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study including smoking history, alcohol use, AJCC stage (per 8th edition), histology, and other relevant history. Participants must be evaluated by the site's multidisciplinary team (eg, medical oncologist, surgeon, radiologist) during screening to assess suitability of participant for the study.
Tumor Sample Submission	X	All participants must have tumor tissue available, either recent archival sample (obtained within 3 months prior to enrollment) or a fresh pre-treatment biopsy obtained during the Screening Period. Sufficient tissue including 1 FFPE tumor block (preferred) or 5-10 unstained slides must be submitted to the central laboratory for PD-L1 testing. The central laboratory must provide IRT with PD-L1 status prior to randomization. See Section 6.1.1 for additional requirements.
Lymph Node Sampling	X	Except for overt cT4 disease, nodal status N2 or N3 must be proven (by biopsy in at least one N2 or N3 node) via endobronchial ultrasound (EBUS), mediastinoscopy, or thoracoscopy. In addition, T3N1 status must be proven in at least one N1 node, if lesion amenable or medically feasible, via one of these modalities. Sample collected prior to screening is acceptable. See Section 6.1 for additional requirements. See Appendix 8 for summary for recommendations for nodal GTV delineation.
Safety Assessments		
Physical Examination (PE), Physical Measurements, and Vital Signs	X	Height, weight, and vital signs (BP, HR, and temperature) must be collected within 14 days prior to randomization.

Table 2-1: Screening Procedural Outline - All Study Arms (Arm A, Arm B, and Arm C) for CA20973L

Procedure	Screening Visit	Notes (28 day window, unless specified otherwise)[a]
ECOG Performance Status	X	Within 14 days prior to randomization (See Appendix 5)
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 14 days prior to randomization. Document vaccine use within 30 days prior to randomization. See Section 7.7.
Serious Adverse Events Assessment	X	Serious Adverse Event collection from time of consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
ECG	X	Must be performed within 14 days prior to randomization. See Section 9.4.3.
Pulmonary function tests	X	FEV1, DLCO (%) within 42 days prior to randomization
Laboratory Tests		
Clinical Laboratory Testing	X	All laboratory assessments to be performed within 14 days prior to randomization, except for viral testing which is to be completed within 28 days prior to randomization. See Table 9.4.4-1 for clinical safety laboratory assessments.
[redacted]		
Pregnancy Test, Follicle Stimulating Hormone Test (FSH)	X	Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at Screening in women of childbearing potential (WOCBP). Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women <55 years of age.
EGFR Mutation	X	EGFR mutation status required for all non-squamous participants (tumor tissue or blood-based assay). Historical results obtained as standard of care prior to Screening Period are acceptable. Testing to be performed locally or centrally. An approved test by local Health Authority is recommended. If mutation testing will be performed centrally, 5 FFPE tumor slides will need to be submitted to the central lab in addition to the 5-10 tumor slides required for PD-L1 testing.

Table 2-1: Screening Procedural Outline - All Study Arms (Arm A, Arm B, and Arm C) for CA20973L

Procedure	Screening Visit	Notes (28 day window, unless specified otherwise)[a]
Tumor Assessments		See Section 9.1
Body Imaging	X	PET/CT Whole Body, including contrast, of the base of skull through the upper thighs within 28 days prior to randomization. PET component can be performed within 42 days prior to randomization. A separate contrast enhanced CT of chest, CT or MRI of upper abdomen (including adrenal glands and full liver), and other suspected sites of disease is required if the CT component of the PET/CT is not of sufficient diagnostic quality for RECIST 1.1 assessments. Participants must have measurable disease per RECIST 1.1 criteria as assessed by investigator. TNM staging according to AJCC 8th edition. See Section 9.1.1 for further details.
Brain Imaging	X	Within 28 days prior to randomization, MRI of the brain without and with contrast is required for ALL participants during screening to rule out brain metastases. CT of the brain (without and with contrast) can be performed if MRI is contraindicated or based on Investigator discretion. See Section 9.1.1 for further details.

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; BP, blood pressure; CRF, case report form; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endobronchial ultrasound; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FEV1, forced expiratory volume during first second of forced breath; FFPE, formalin-fixed paraffin-embedded; FSH, follicle-stimulating hormone; GTV, gross tumor volume; HCG, human chorionic gonadotropin; [redacted]; IRT, Interactive Response Technology; MRI, magnetic resonance imaging; PD-L1, programmed death-ligand 1; PE, physical examination; PET, positron emission tomography; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; [redacted]; TNM, tumor nodal metastasis; WOCBP, women of childbearing potential.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Safety Assessments														
Targeted Physical Examination, Weight, and Vital Signs	X			X					X					Weight, BP, HR, and temperature before treatment on D1 of each cycle. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance Status	X			X					X					Prior to treatment on D1 of each cycle. See Appendix 5
Adverse Events Assessment (including Serious Adverse Events)	Continuously													All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Record at each visit. Collect continuously throughout the CCRT Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously													Record at each visit.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Laboratory Tests														
Clinical Laboratory Testing	X			X					X					Within 72 hrs prior to dosing. Note: C1D1 labs (or C2D1 labs for participants who skip cycle 1; see footnote a) do not need to be repeated if performed at screening within 72 hours prior to the start of treatment. See Table 9.4.4-1 for clinical safety laboratory assessments.
Thyroid Stimulating Hormone	X			X					X					TSH (with reflexive fT3 and fT4 if TSH is abnormal) must be performed within 72 hrs prior to D1 of every cycle **except for Arm C in the CCRT period**. Note: C1D1 labs (or C2D1 labs for participants who skip C1; see footnote a) do not need to be repeated if performed at screening within 72 hours prior to the start of treatment. For more details, see Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP only	X			X					X					Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to Day 1 of each cycle. Test must be performed at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
PK/ IMG Assessments (Arm A and Arm B only)	PK and immunogenicity sampling varies by cycle. See specimen collection schedule as specified in Arm A (CCRT) in Table 9.5-1 and Arm B (CCRT) in Table 9.5-3.													See Section 9.5 for complete details.
[redacted]														
Outcomes Assessments														
NSCLC-SAQ	X			X					X					Completed prior to dosing on D1 of each cycle. If a dose is delayed, outcome assessments should also be delayed until dosing is resumed. See Section 9.1.2.
PGI-S	X			X					X					
FACT-L	X			X					X					
EQ-5D-5L	X			X					X					
Healthcare Resource Utilization (HCRU)	X			X					X					See Section 9.9.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Study Treatment														See Section 7.1.
Randomize	X			**See note**										Up to 7 days prior to C1D1 (**Note**: C2D1 for participants who skip cycle 1; see footnote a). Prior to randomization, the planned chemotherapy regimen, the planned number of cycles of chemotherapy (up to 2 cycles or up to 3 cycles), the planned dose level of chemotherapy at the start of treatment for agents with more than 1 possible dose level per protocol (e.g. carboplatin, paclitaxel), and the radiation modality must be pre-defined and documented in the IRT and medical records by the investigator.
Administer Nivolumab (**Arm A and Arm B Only**)	X			X					X					**Participants in Arm C will not receive nivolumab as part of the CCRT Period** Administer nivolumab for participants randomized to Arms A and B only as a flat dose of 360 mg IV Q3W on Day 1 of each cycle. Nivolumab must be administered prior to administration of chemotherapy.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Administer Cisplatin (or Carboplatin) (all Arms)	X			X					X					First dose of chemotherapy must be administered within 7 calendar days of randomization. If a participant cannot tolerate cisplatin, then carboplatin may be used at dose of AUC 5 IV Q3W on Day 1 of each cycle at the discretion of the investigator. Pre-medication prior to the chemotherapy on D1 of each cycle should be administered after the completion of nivolumab infusion (Arms A and B). Cisplatin (or carboplatin) treatment outlined here is for combination with pemetrexed or etoposide only.
Administer Etoposide (**only for participants NOT receiving Pemetrexed**)	X	X	X	X	X	X			X	X	X			**For participants receiving cisplatin (or carboplatin) and Etoposide:** Cisplatin must be administered as a dose of 80 mg/m^2 IV Q3W on Day 1 of each cycle. Etoposide must be administered as a dose of 100 mg/m^2 IV Q3W on a Day 1, Day 2, and Day 3 of each cycle. Days 2 and 3 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment and per investigator's discretion.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Administer Pemetrexed (**only for participants NOT receiving Etoposide**)	X			X					X					**For participants receiving cisplatin (or carboplatin) and Pemetrexed:** Cisplatin must be administered as a dose of 75 mg/m^2 IV Q3W on Day 1 of each cycle. Pemetrexed must be administered with a dose of 500 mg/m^2 IV Q3W on a Day 1 of each cycle. If a participant cannot tolerate pemetrexed, then etoposide may be used instead at the discretion of the investigator.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Radiotherapy				Radiation therapy starts on Day 1 of Cycle 2 **(See note)** Participants will receive radiotherapy for 5 days every week in daily fraction of 2 Gy. The total target dose will be 60-66 Gy in 30-33 fractions										Each participant will receive thoracic radiotherapy in form of IMRT, VMAT, or 3DRT. The order of the treatment for D1 of C2 and C3 are nivolumab, followed by chemotherapy. It is recommended that radiotherapy be administered after the completion of systemic anti-cancer therapy and on the same day if logistically feasible. Otherwise, a window of ± 3 days is permitted. **Note:** If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 (Arms A, B or C), the Investigator has the option to skip Cycle 1 procedures (with systemic anticancer therapy alone) and initiate the CCRT period with Cycle 2 procedures (radiotherapy concurrently with systemic anticancer therapy). All study procedures for Cycle 2 and Cycle 3 are still to be followed in this situation.

Table 2-2: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Treatment Regimens

Procedure	Cycle 1[a,b] (3 weeks)			Cycle 2[a,b] (3 weeks ± 3 days)					Cycle 3[b] (3 weeks ± 3 days)					Notes[c]
	D1	D2	D3	D1	D2	D3	D4	D5	D1	D2	D3	D4	D5	
Efficacy Assessments														
Body and/or Brain Imaging	See note													No scheduled scan until the recovery period but unscheduled scans are permitted per investigator judgment. For participants with progressive disease that has not been confirmed by BICR, if the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Abbreviations: 3DRT, 3-dimensional radiotherapy; AE, adverse event; AUC, area under the concentration-time curve; BICR, blinded independent central review; BP, blood pressure; C, Cycle; CCRT, concurrent chemoradiotherapy; CRF, case report form; D, day; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted]; fT3, free triiodothyronine; fT4, free thyroxine; HCG, human chorionic gonadotropin; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; IMG, immunogenicity; IMRT, intensity-modulated radiation therapy; IRT, Interactive Response Technology; IV, intravenous; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; Q3W, every 3 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSH, thyroid stimulating hormone; VMAT, volumetric-modulated arc therapy; WOCBP, women of childbearing potential.

[a] If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT period (Arms A, B or C), the Investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. The Recovery Period will begin after the final dose of radiotherapy and the completion of Cycle 3 procedures as outlined above. An additional cycle of consolidation chemotherapy + nivolumab (Arms A and B) or chemotherapy alone (Arm C) will **not** be administered after the completion of radiotherapy in this situation.

[b] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Carboplatin + Paclitaxel Treatment Regimen

Procedure	Cycle 1[a,b] (3 weeks)	Cycle 2[a,b] (3 weeks ± 3 days)			Cycle 3[b] (3 weeks ± 3 days)			Notes[c]
	D1	D1	D8	D15	D1	D8	D15	
Safety Assessments								
Targeted PE, Weight, and Vital Signs	X	X	X	X	X	X	X	Weight, BP, HR, and temperature before treatment. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance Status	X	X	X	X	X	X	X	See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously							All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Record at each visit. Collect continuously throughout the CCRT Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously							Record at each visit.
Laboratory Tests								
Clinical Laboratory Testing	X	X	X	X	X	X	X	Within 72 hrs prior to dosing. Note: C1D1 labs (or C2D1 labs for participants who skip cycle 1; see footnote a) do not need to be repeated if performed at screening within 72 hours prior to the start of treatment. See Table 9.4.4-1 for clinical safety laboratory assessments.

Table 2-3: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Carboplatin + Paclitaxel Treatment Regimen

Procedure	Cycle 1[a,b] (3 weeks)	Cycle 2[a,b] (3 weeks ± 3 days)			Cycle 3[b] (3 weeks ± 3 days)			Notes[c]
	D1	D1	D8	D15	D1	D8	D15	
Thyroid Stimulating Hormone	X	X			X			TSH (with reflexive fT3 and fT4 if TSH is abnormal) must be performed within 72 hrs prior to D1 of every cycle **except for Arm C in the CCRT period**. Note: C1D1 labs (or C2D1 labs for participants who skip C1; see footnote a) do not need to be repeated if performed at screening within 72 hours prior to the start of treatment. See Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test (WOCBP only)	X	X			X			Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to Day 1 of each cycle. Test must be performed at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.
PK/ IMG Assessments (Arm A and Arm B only)	PK and immunogenicity sampling varies by cycle. See specimen collection schedule as specified in Arm A (CCRT) in Table 9.5-1 and Arm B (CCRT) in Table 9.5-3.							See Section 9.5 for complete details.
[redacted]								

Table 2-3: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Carboplatin + Paclitaxel Treatment Regimen

Procedure	Cycle 1[a,b] (3 weeks)	Cycle 2[a,b] (3 weeks ± 3 days)			Cycle 3[b] (3 weeks ± 3 days)			Notes[c]
	D1	D1	D8	D15	D1	D8	D15	
Outcomes Assessments								
NSCLC-SAQ	X	X			X			Completed prior to dosing on D1 of each cycle. If a dose is delayed, outcome assessments should also be delayed until dosing is resumed. See Section 9.1.2.
PGI-S	X	X			X			
FACT-L	X	X			X			
EQ-5D-5L	X	X			X			
HCRU	X	X			X			See Section 9.9.
Study Treatment								See Section 7.1.
Randomize	X	**See notes**						Up to 7 days prior to C1D1 (**Note:** or C2D1 for participants who skip cycle 1; see footnote a). Prior to randomization, the planned chemotherapy regimen, the planned number of cycles of chemotherapy (up to 2 cycles or up to 3 cycles), the planned dose level of chemotherapy at the start of treatment for agents with more than 1 possible dose level per protocol (e.g. carboplatin, paclitaxel), and the radiation modality must be pre-defined and documented in the IRT and medical records by the investigator.
Administer Nivolumab (**Arm A and Arm B Only**)	X	X			X			**Participants in Arm C will not receive nivolumab as part of the CCRT Period** Administer nivolumab for participants randomized to Arms A and B only as a flat dose of 360 mg IV Q3W on Day 1 of each cycle. Nivolumab must be administered prior to administration of chemotherapy.

Table 2-3: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Carboplatin + Paclitaxel Treatment Regimen

Procedure	Cycle 1[a,b] (3 weeks)	Cycle 2[a,b] (3 weeks ± 3 days)			Cycle 3[b] (3 weeks ± 3 days)			Notes[c]
	D1	D1	D8	D15	D1	D8	D15	
Administer Carboplatin (**only when used in combination with Paclitaxel**)	X	X	X	X	X	X	X	First dose of chemotherapy must be administered within 7 calendar days of randomization. Days 8 and 15 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment and per investigator's discretion. Pre-medication prior to the chemotherapy on D1 of each cycle should be administered after the completion of nivolumab infusion, if clinically feasible (Arms A and B). **Carboplatin is to be administered as follows in combination with paclitaxel:** • AUC 5 or 6 on Day 1 of Cycle 1 • AUC 2 on Days 1, 8, and 15 of Cycle 2 and Cycle 3
Administer Paclitaxel	X	X	X	X	X	X	X	First dose of chemotherapy must be administered within 7 calendar days of randomization. Days 8 and 15 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment and per investigator's discretion. **Paclitaxel is to be administered as follows in combination with carboplatin:** • 175 or 200 mg/m^2 on Day 1 of Cycle 1 • 45 or 50 mg/m2 on Days 1, 8, and 15 of Cycle 2 and Cycle 3

Table 2-3: On Study Treatment Procedural Outline – Concurrent Chemoradiotherapy (CCRT) Period – All Arms (Arm A, Arm B, and Arm C for CA20973L) Carboplatin + Paclitaxel Treatment Regimen

Procedure	Cycle 1[a,b] (3 weeks)	Cycle 2[a,b] (3 weeks ± 3 days)			Cycle 3[b] (3 weeks ± 3 days)			Notes[c]
	D1	D1	D8	D15	D1	D8	D15	
Radiotherapy		Radiation therapy starts on Day 1 of Cycle 2. **See note.** Participants will receive radiotherapy for 5 days every week in daily fraction of 2 Gy. The total target dose will be 60-66 Gy in 30-33 fractions						Each participant will receive thoracic radiotherapy in form of IMRT, VMAT, or 3DRT. The order of the treatment for D1 of C2 and C3 are nivolumab, followed by chemotherapy. It is recommended that radiotherapy be administered after the completion of systemic anticancer therapy and on the same day if logistically feasible. Otherwise, a window of ± 3 days is permitted. **Note:** If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 (Arms A, B or C), the Investigator has the option to skip Cycle 1 procedures (with systemic anticancer therapy alone) and initiate the CCRT period with Cycle 2 procedures (radiotherapy concurrently with systemic anticancer therapy). All study procedures for Cycle 2 and Cycle 3 are still to be followed in this situation.
Efficacy Assessments								
Body and/or Brain Imaging		**See note.**						No scheduled scan until the recovery period but unscheduled scans are permitted per investigator judgment. For participants with progressive disease that has not been confirmed by BICR, if the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Abbreviations: 3DRT, 3-dimensional radiotherapy; AE, adverse event; AUC, area under the concentration-time curve; BICR, blinded independent central review; BP, blood pressure; C, Cycle; CCRT, concurrent chemoradiotherapy; CRF, case report form; D, day; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted] fT3, free triiodothyronine; fT4, free thyroxine; HCG, human chorionic gonadotropin; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; IMG, immunogenicity; IMRT, intensity-modulated radiation therapy; IRT, Interactive Response Technology; IV, intravenous; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PE, physical examination; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; Q3W, every 3 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSH, thyroid stimulating hormone; VMAT, volumetric-modulated arc therapy; WOCBP, women of childbearing potential.

[a] If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT period (Arms A, B or C), the Investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. The Recovery Period will begin after the final dose of radiotherapy and the completion of Cycle 3 procedures as outlined above. An additional cycle of consolidation chemotherapy + nivolumab (Arms A and B) or chemotherapy alone (Arm C) will **not** be administered after the completion of radiotherapy in this situation.

[b] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 2-4: On Study Treatment Procedural Outline – Recovery Period – All Arms (CA20973L)

Procedure	Recovery Period		Notes
	Week 3 of Recovery Period Day 22 post CCRT	End of Recovery Period[a]	
Safety Assessments			
Targeted PE, Weight, and Vital Signs	X	X	Weight, BP, HR, and temperature
ECOG Performance Status	X	X	See Appendix 5.
ECG		X	
Adverse Events Assessment (including SAEs)	Continuously		All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the recovery period. Record at each visit. Collect continuously throughout the Recovery Period. See Section 9.2.
Concomitant Medication Use	Continuously		Record at each visit.
Laboratory Tests			
Clinical Laboratory Testing	X	X	Hematology and chemistry testing should be collected during Recovery Period and before maintenance treatment. All testing results during the Recovery Period should be documented. See Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test (WOCBP only)	See notes		Serum or urine pregnancy test must be performed at least every 4 weeks (± 1 week) during Recovery Period.
Eligibility Criteria before Entering the Maintenance Period		X	See Section 6.1.2 and Section 6.2.2.

Table 2-4: On Study Treatment Procedural Outline – Recovery Period – All Arms (CA20973L)

Procedure	Recovery Period		Notes
	Week 3 of Recovery Period Day 22 post CCRT	End of Recovery Period[a]	
Efficacy Assessments			
Body Imaging[b]	X		First on-study scans are expected during the Week 3 visit in the Recovery Period. Contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and all other known and/or suspected sites of disease should be performed during approximately the Week 3 visit in Recovery Period. Use same imaging method as was used at screening. See Section 9.1.1 for further details.
Brain Imaging[b]	See notes		MRI of the brain without and with contrast if clinically indicated. CT of the brain (without and with contrast) can be performed if MRI is contraindicated or based on Investigator discretion. See Section 9.1.1 for further details.
Outcomes Assessments			
NSCLC-SAQ	X	X	Complete at beginning of each clinic visit during Recovery Period including the End of Recovery visit. See Section 9.1.2 for further details.
PGI-S	X	X	
FACT-L	X	X	
EQ-5D-5L	X	X	
HCRU	X	X	See Section 9.9.

Abbreviations: AE, adverse event; BP, blood pressure; CCRT, concurrent chemoradiotherapy; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; HR, heart rate; HCRU, healthcare resource utilization; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PE, physical examination; PGI-S, Patient Global Impression of Severity; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] Recovery Period will last approximately 3 to 6 weeks after completion of CCRT (ie, last dose of radiotherapy). If further delay (> 6 weeks) is needed, approval by medical monitor or designee is required to move on to the maintenance period, and this must be documented in the participant's medical record. See Section 5.1.3 for details on the Recovery Period. If participant appears fully recovered at approximately the Week 3 visit, then all procedures required at End of Recovery Period may be performed at approximately the Week 3 visit. The approximately Week 3 visit will then be considered the End of Recovery Period visit. All safety assessments performed post week 3 during Recovery Period should be documented in the eCRFs or via external data transfer. Collection of outcome assessments should only be done once when more than one study visit occurs on the same day. If participant discontinues at the End of Recovery visit, the End of Recovery Visit may be considered as safety Follow-up 1 visit. If participant meets eligibility criteria of entering into maintenance period within 2 weeks from the end of CCRT (ie, last dose of radiotherapy), maintenance treatment may be initiated earlier but no less than 18 days after the last dose of nivolumab (Arm A and Arm B). If participant meets eligibility criteria of entering into maintenance period but beyond Recovery Period window, approval by Medical Monitor or designee is needed and must be documented in medical record.

[b] If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Table 2-5: On Study Treatment Procedural Outline – Maintenance Period – Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]		Cycle 2 (Maintenance) and beyond[a] (6 weeks ± 3 days)		Notes:[b] Cycle = 6 weeks
	D1[c]	D22	D1	D22	
Safety Assessments					
Targeted PE, Weight, Vital Signs	X	X	X	X	Weight, BP, HR, and temperature before treatment. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance status	X		X		To be performed prior to treatment on D1. See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously				All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Record at each visit. Collect continuously throughout the Maintenance Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously				Record at each visit.
Laboratory Tests					
Clinical Laboratory Testing	X	X	X	X	Must be performed within 72 hrs prior to dosing. C1D1 labs do not need to be repeated if performed in the end of Recovery Period and within 72 hrs of C1D1 dosing. See Table 9.4.4-1 for clinical safety laboratory assessments.
Thyroid Stimulating Hormone	X		X		TSH (with reflexive fT3 and fT4 if TSH is abnormal) must be performed within 72 hrs prior to D1 of every cycle. For more details, see Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP only	X	X	X	X	Serum or urine pregnancy test must be performed within 72 hours before each dose or at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-5: On Study Treatment Procedural Outline – Maintenance Period – Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]		Cycle 2 (Maintenance) and beyond[a] (6 weeks ± 3 days)		Notes:[b] Cycle = 6 weeks
	D1[c]	D22	D1	D22	
Efficacy Assessments					
Body Imaging[d]			See note		Contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease should be performed at week 24 (±7 days) from the date of randomization, then every 12 weeks (±7 days) during treatments. During treatment beyond progression (TBP), a follow up scan is required within 6 weeks of initial Investigator-assessed PD to determine if there has been a reduction in tumor size, SD, or continued progression. If TBP continues beyond the 6 week scan (based on Investigator judgment), subsequent scans should be performed every 12 weeks (±7 days), or if additional worsening is suspected. Other anatomical sites should be imaged in the presence of signs or symptoms suggesting disease progression. Tumor assessment schedule should be maintained regardless of dose delays. Tumor assessments will continue until BICR confirmed disease progression, Investigator-assessed distant metastases, or treatment discontinuation due to additional PD during treatment beyond progression (TBP), whichever occurs later. Use same imaging method as was used at screening. All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.1.2 for additional details.
Brain Imaging[d]			See note		To be performed as clinically indicated for suspicion of disease. See Section 9.1.1.2 for additional details.
PK/Immunogenicity Assessments	PK and immunogenicity sampling schedule specified in Table 9.5-2				See Section 9.5 for complete details.
[redacted]					

Table 2-5: On Study Treatment Procedural Outline – Maintenance Period – Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]		Cycle 2 (Maintenance) and beyond[a] (6 weeks ± 3 days)		Notes:[b] Cycle = 6 weeks
	D1[c]	D22	D1	D22	
Outcomes Assessments					
NSCLC-SAQ	X		X		To be completed prior to treatment at the start of each maintenance cycle. If a dose is delayed, outcome assessments should also be delayed until dosing is resumed. See Section 9.1.2 for further details.
PGI-S	X		X		
FACT-L	X		X		
EQ-5D-5L	X		X		
HCRU	X		X		See Section 9.9.
Study Treatment					After participants complete Recovery Period, the first dose must be administered within 3 calendar days and no less than 18 days from the last dose of nivolumab. Maintenance Period will last approximately 12 months with each treatment cycle lasting 6 weeks.
Nivolumab Q3W	X	X	X	X	Nivolumab 360 mg administered on D1 and D22 of each cycle. See Section 7.1.1.
Ipilimumab Q6W	X		X		Ipilimumab 1 mg/kg administered on D1 of each cycle. Participant baseline weight at C1D1 or within 3 days prior to entering the Maintenance Period should be used for ipilimumab dosing calculation. A ≥ 10% change in weight from baseline requires recalculation for weight-based dosing. See Section 7.1.2 for further details.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; C, cycle; CRF, case report form; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted]; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD, progressive disease; PE, physical examination; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; Q3W, every 3 weeks; Q6W, every 6 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, stable disease; TBP, treatment beyond pregression; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[b] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

[c] Safety assessments on C1D1 do not need to be repeated if performed within 3 days of C1D1 at End of Recovery Period.

[d] If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Table 2-6: On Study Treatment Procedural Outline – Maintenance Period – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a] (4 weeks ± 3 days)	Notes:[b] Cycle = 4 weeks
	D1[c]	D1	
Safety Assessments			
Targeted PE, Weight, and Vital Signs	X	X	Weight, BP, HR, and temperature prior to treatment. Weight can be assessed up to 24 hours prior to dosing
ECOG Performance Status	X	X	To be performed prior to treatment on D1. See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously		All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Record at each visit. Collect continuously throughout the Maintenance Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously		Record at each visit
Laboratory Tests			
Clinical Laboratory Testing	X	X	To be performed within 72 hrs prior to dosing. See Table 9.4.4-1 for clinical safety laboratory assessments. C1D1 labs do not need to be repeated if end of Recovery labs were performed within 72 hrs of dosing.
Thyroid Stimulating Hormone	X	X	TSH (with reflexive fT3 and fT4 if TSH is abnormal) must be performed within 72 hrs prior to D1 of every cycle. For more details, see Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP	X	X	Serum or urine pregnancy test must be performed within 72 hours before each dose or at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-6: On Study Treatment Procedural Outline – Maintenance Period – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a] (4 weeks ± 3 days)	Notes:[b] Cycle = 4 weeks
	D1[c]	D1	
Efficacy Assessments			
Body Imaging[d]		See note	Contrast enhanced CT of Chest , CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease should be performed at week 24 (±7 days) from the date of randomization, then every 12 weeks (±7 days) during treatment. During treatment beyond progression (TBP), a follow up scan is required within 6 weeks of initial Investigator-assessed PD to determine if there has been a reduction in tumor size, SD, or continued progression. If TBP continues beyond the 6 week scan (based on Investigator judgment), subsequent scans should be performed every 12 weeks (±7 days), or if additional worsening is suspected. Other anatomical sites should be imaged in the presence of signs or symptoms suggesting disease progression. Tumor assessment schedule should be maintained regardless of dose delays. Tumor assessments will continue until BICR confirmed disease progression, Investigator-assessed distant metastases, or treatment discontinuation due to additional PD during TBP, whichever occurs later. Use same imaging method as was used at screening. All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.1.2 for additional details.
Brain Imaging[d]		See note	To be performed as clinically indicated for suspicion of disease. See Section 9.1.1.2 for additional details.
PK/Immunogenicity Assessments	PK and Immunogenicity sampling schedule specified in Table 9.5-4.		See Section 9.5 for complete details.

Table 2-6: On Study Treatment Procedural Outline – Maintenance Period – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a] (4 weeks ± 3 days)	Notes:[b] Cycle = 4 weeks
	D1[c]	D1	
[redacted]			
Outcomes Assessments			
NSCLC-SAQ	X	X	To be completed prior to treatment at the start of each maintenance cycle. If a dose delay occurs, outcome assessments should also be delayed until dosing is resumed. See Section 9.1.2 for further details.
PGI-S	X	X	
FACT-L	X	X	
EQ-5D-5L	X	X	
HCRU	X	X	See Section 9.9.
Study Treatment			After participants complete Recovery Period, the first dose must be administered within 3 calendar days and no less than 18 days from the last dose of nivolumab. Maintenance Period will last approximately 12 months with each treatment cycle lasting 4 weeks.
Nivolumab Q4W	X	X	Nivolumab 480 mg administered on D1 of each cycle. Participants may be dosed no less than 25 days from the previous dose of nivolumab during Q4W cycles. See Section 7.1.1.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; C, cycle; CRF, case report form; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted]; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD, progressive disease; PE, physical examination; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetic; Q4W, every 4 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, stable disease; TBP, treatment beyond progression; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[b] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

[c] Safety assessments on C1D1 do not need to be repeated if performed within 3 days of C1D1 at End of Recovery Period.

[d] If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Table 2-7: On Study Treatment Procedural Outline – Maintenance Period – Arm C (Durvalumab Q2W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a]	Notes:[b] (Cycle = 2 weeks ± 3 days)
	D1[c]	D1	
Safety Assessments			
Targeted PE, Weight, and Vital Signs	X	X	Weight, BP, HR, and temperature prior to treatment. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance Status	X	X	To be performed prior to treatment. See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously		All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Record at each visit. Collect continuously throughout the Maintenance Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously		Record at each visit.
Laboratory Tests			
Clinical Laboratory Testing	X	X	To be performed within 72 hours prior to dosing. C1D1 labs do not need to be repeated if end of Recovery labs were performed within 72 hrs of C1D1 dosing. See Table 9.4.4-1 for clinical safety laboratory assessments.
Thyroid Stimulating Hormone	X	X	TSH (with reflexive fT3 and fT4 if TSH is abnormal) must be performed within 72 hrs prior to D1 of every cycle. For more details, see Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP	X	X	Serum or urine pregnancy test must be performed within 72 hours before each dose or at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-7: On Study Treatment Procedural Outline – Maintenance Period – Arm C (Durvalumab Q2W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a]	Notes:[b] (Cycle = 2 weeks ± 3 days)
	D1[c]	D1	
Efficacy Assessments			
Body Imaging[d]		See note	Contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease should be performed at week 24 (± 7 days) from the date of randomization, then every 12 weeks (± 7 days) during treatment. During treatment beyond progression (TBP), a follow up scan is required within 6 weeks of initial Investigator-assessed PD to determine if there has been a reduction in tumor size, SD, or continued progression. If TBP continues beyond the 6 week scan (based on Investigator judgment), subsequent scans should be performed every 12 weeks (± 7 days), or if additional worsening is suspected. Other anatomical sites should be imaged in the presence of signs or symptoms suggesting disease progression. Tumor assessment schedule should be maintained regardless of dose delays. Tumor assessments will continue until BICR confirmed disease progression, Investigator-assessed distant metastases, or treatment discontinuation due to additional PD during TBP, whichever occurs later. Use same imaging method as was used at screening. All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.1.2 for additional details.
Brain Imaging[d]		See note	To be performed as clinically indicated for suspicion of disease. See Section 9.1.1.2 for additional details.
[redacted]			

Table 2-7: On Study Treatment Procedural Outline – Maintenance Period – Arm C (Durvalumab Q2W) (CA20973L)

Procedure	Cycle 1 (Maintenance)[a]	Cycle 2 (Maintenance) and beyond[a]	Notes:[b] (Cycle = 2 weeks ± 3 days)
	D1[c]	D1	
Outcomes Assessments			
NSCLC-SAQ	See notes		To be completed prior to treatment at the start of maintenance cycle at: C1, C3, C4, C5, C7, C9, C10, C11, C13, C15, C16, C17, C19, C21, C22, C23, and C25. If a dose is delayed, outcome assessments should also be delayed until dosing is resumed. See Section 9.1.2 for further details.
PGI-S			
FACT-L			
EQ-5D-5L			
HCRU	X	X	See Section 9.9.
Study Treatment			After participants complete Recovery Period, the first dose must be administered within 3 calendar days. Maintenance Period will last approximately 12 months with each treatment cycle lasting 2 weeks.
Durvalumab Q2W	X	X	Durvalumab 10 mg/kg administered on D1 of each cycle. The participant's baseline weight at C1D1 or within 3 days prior to entering the Maintenance Period must be used for durvalumab dosing calculation. From C2D1 and onwards, dosing should be calculated based on the weight assessed prior to each dosing or per local approved label. See Section 7.1.3.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; C = cycle; CRF, case report form; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted]; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD, progressive disease; PE, physical examination; PGI-S, Patient Global Impression of Severity; Q2W, every 2 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, stable disease; TBP, treatment beyond progression; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[b] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

[c] Safety assessments on C1D1 do not need to be repeated if performed within 3 days of C1D1 at End of Recovery Period.

[d] If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Table 2-8: Follow-Up Period – All Arms (CA20973L)

Procedure	Safety Follow-Up Visit 1[a] 30 Days from Last Dose (± 7 Days)	Safety Follow-Up Visit 2[a] 100 days from Last Dose (± 7 Days)	Tumor Assessments Every 3-6 months (± 7 days)	Survival Follow-Up[a] Every 3 months from Follow-Up Visit 2 (± 14 days)	Notes[b]
Safety Assessments					
Targeted Physical Examination, Weight, and Vital Sign	X	X			Weight, BP, HR, and temperature.
ECOG Performance Status	X	X			See Appendix 5.
Adverse Events Assessment (including SAEs)	X	X	See notes	See notes	All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of dosing. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out. Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. See Section 9.2 for additional information.

Table 2-8: Follow-Up Period – All Arms (CA20973L)

Procedure	Safety Follow-Up Visit 1[a] 30 Days from Last Dose (± 7 Days)	Safety Follow-Up Visit 2[a] 100 days from Last Dose (± 7 Days)	Tumor Assessments Every 3-6 months (± 7 days)	Survival Follow-Up[a] Every 3 months from Follow-Up Visit 2 (± 14 days)	Notes[b]
Concomitant Medication Use	X	X		See note	In Survival Follow-up, subsequent cancer treatment only.
Laboratory Tests					
Clinical Laboratory Testing	X	See Notes			To be performed at Safety Follow-up Visit 2, if toxicities remain. See Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP	X	X			
[redacted]					

Table 2-8: Follow-Up Period – All Arms (CA20973L)

Procedure	Safety Follow-Up Visit 1[a] 30 Days from Last Dose (± 7 Days)	Safety Follow-Up Visit 2[a] 100 days from Last Dose (± 7 Days)	Tumor Assessments Every 3-6 months (± 7 days)	Survival Follow-Up[a] Every 3 months from Follow-Up Visit 2 (± 14 days)	Notes[b]
Efficacy Assessments					
Body Imaging[c,d]			See notes		In Follow-up Period, participants without BICR-confirmed progression and/or Investigator-assessed distant metastases only will receive contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease • every 12 weeks (±7 days) for up to and including 36 months from date of randomization, • then every 24 weeks (±7 day) after month 36 from date of randomization. Other anatomical sites should be imaged in the presence of signs or symptoms suggesting disease progression. Tumor assessments will continue until BICR confirmed disease progression or Investigator-assessed distant metastases, whichever occurs later. Use the same imaging method as was used at Screening. See Section 9.1.1.2 for additional details.
Brain Imaging[c,d]			See notes		In Follow-up Period, brain imaging is only required for participants without BICR-confirmed progression and/or Investigator assessed distant metastases. To be performed as clinically indicated for suspicion of disease. See Section 9.1.1.2 for additional details.

Table 2-8: Follow-Up Period – All Arms (CA20973L)

Procedure	Safety Follow-Up Visit 1[a] 30 Days from Last Dose (± 7 Days)	Safety Follow-Up Visit 2[a] 100 days from Last Dose (± 7 Days)	Tumor Assessments Every 3-6 months (± 7 days)	Survival Follow-Up[a] Every 3 months from Follow-Up Visit 2 (± 14 days)	Notes[b]
Survival Status	X	X		X	Survival Follow-up visits to occur every 3 months (±14 days) from Safety Follow-up Visit 2. Survival visits may be conducted in person or by telephone (phone contact is an option after BICR confirmed PD and Investigator assessed distant metastases, or after month 36 from date of randomization if not coinciding with a tumor assessment visit). BMS may request that survival data are collected on all treated participants outside of the 3 month window.
Subsequent PD (PFS-2)	X	X	X	X	For participants who start subsequent anticancer therapy, subsequent PD date and diagnosis method during subsequent treatment will be recorded on the CRF during the Follow-up Period. Subsequent PD assessment takes participant status at 1st PD (per Investigator assessment) as re-baseline, is defined per local standard practice, and may entail radiological PD, clinical PD, or other.

Table 2-8: Follow-Up Period – All Arms (CA20973L)

Procedure	Safety Follow-Up Visit 1[a] 30 Days from Last Dose (± 7 Days)	Safety Follow-Up Visit 2[a] 100 days from Last Dose (± 7 Days)	Tumor Assessments Every 3-6 months (± 7 days)	Survival Follow-Up[a] Every 3 months from Follow-Up Visit 2 (± 14 days)	Notes[b]
Subsequent Anticancer Therapy[d]	X	X	X	X	Following Investigator-assessed PD, participants will be discontinued from treatment and assessed at survival follow-up visits (every 3 months) for subsequent progression (ie, PFS-2). Information on the subsequent PD, subsequent anticancer therapy and outcome must be collected. Additional subsequent cancer therapy information such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy will be collected.
Outcomes Assessments					
NSCLC-SAQ	X	X	X		Assessments will be collected on Safety Follow up Visit 1 and 2 for all participants. For participants who complete/discontinue from the Maintenance Period, continue at every tumor assessment visit until BICR confirmed disease progression. In addition, EQ-5D-5L to be collected at every survival visit which is not associated with tumor assessment visits, including phone contact for the survival. Outcome assessments will not be performed during the re-treatment follow-up period.
PGI-S	X	X	X		
FACT-L	X	X	X		
EQ-5D-5L	X	X	X	X	
HCRU	X	X	X		See Section 9.9 for further details.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BMS, Bristol-Myers Squibb; BP, blood pressure; CRF, case report form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; [redacted]; HCRU, healthcare resource utilization; HR, heart rate; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD, progressive disease; PFS-2, progression-free survival on next line therapy; PGI-S, Patient Global Impression of Severity; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after the last dose of study treatment. Safety Follow-up Visit 1 should occur 30 days from the last dose (± 7 days). If participant delays treatment and later discontinues treatment > 42 days from the last treatment, the Safety Follow-up Visit 1 may be performed at time of discontinuation. Safety Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of study treatment. Both follow-up visits should be conducted in person.

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

[c] See Section 5.1.6 for imaging requirements after retreatment period.

[d] If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy.

Table 2-9: Optional Retreatment Procedural Outline - Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 Retreatment[b]		Cycle 2 Retreatment and beyond[b] (6 weeks ± 3 days)		Notes: Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	D1	D22	D1	D22	
Informed Consent	X					Participants must be re-consented for retreatment.
Eligibility Assessment	X	X				See Section 5.1.6.
Safety Assessments						
Targeted PE, Weight, Vital Signs	X	X	X	X	X	Weight, BP, HR, and temperature before treatment. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance status	X	X		X		To be performed prior to treatment on D1. See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously					Record at each visit. Collect continuously throughout the Retreatment Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously					Record at each visit.
Laboratory Tests						
Clinical Laboratory Testing	X	X	X	X	X	Must be performed within 72 hrs prior to dosing. Retreatment C1D1 labs do not need to be repeated if performed in the initial Follow-up Period and within 72 hrs prior to retreatment C1D1 dosing. See Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP only	X	X	X	X	X	Serum or urine pregnancy test must be performed within 72 hours before each dose or at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-9: Optional Retreatment Procedural Outline - Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 Retreatment[b]		Cycle 2 Retreatment and beyond[b] (6 weeks ± 3 days)		Notes: Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	D1	D22	D1	D22	
Efficacy Assessments						
Body Imaging	X			See note		Contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease should be performed at every 12 weeks (±7 days) from BICR confirmed initial disease progression (starting from date of scan). Tumor assessment schedule should be maintained regardless of dose delays. Scans do not need to be submitted to BICR. Subsequent PD during the Retreatment Period will be per investigator's assessment. Treatment beyond second progression is not allowed. Participants without Investigator-assessed distant metastases must continue tumor scans during the Retreatment Period until metastasis is assessed by the Investigator. Use same imaging method used at screening. All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 5.1.6 and Section 9.1.1.2 for additional details.
Brain Imaging	X			See note		To be performed as clinically indicated for suspicion of disease. Scans do not need to be submitted to BICR. Subsequent PD during the Retreatment Period will be per investigator's assessment. Treatment beyond second progression is not allowed. See Section 5.1.6 and Section 9.1.1.2 for additional details.

Table 2-9: Optional Retreatment Procedural Outline - Arm A (Nivolumab Q3W + Ipilimumab Q6W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 Retreatment[b]		Cycle 2 Retreatment and beyond[b] (6 weeks ± 3 days)		Notes: Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	D1	D22	D1	D22	
Study Treatment						Participants who enter the Follow-up Period with ongoing disease control (CR, PR, or SD) and without a history of treatment beyond progression, may receive retreatment in Arm A upon BICR confirmed disease progression. Retreatment Period will last up to 12 months with each treatment cycle lasting 6 weeks.
Nivolumab Q3W		X	X	X	X	Nivolumab 360 mg administered on D1 and D22 of each cycle. See Section 7.1.1.
Ipilimumab Q6W		X		X		Ipilimumab 1 mg/kg administered on D1 of each cycle. Participant baseline weight at C1D1 or within 3 days prior to entering the Retreatment Period should be used for ipilimumab dosing calculation. A ≥ 10% change in weight from baseline requires recalculation for weight-based dosing. See Section 7.1.2 for further details.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; C, cycle; CR, complete response; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MRI, magnetic resonance imaging; PD, progressive disease; PE, physical examination; PR, partial response; Q3W, every 3 weeks; Q6W, every 6 weeks; SAE, serious adverse event; SD, stable disease; WOCBP, women of childbearing potential.

[a] Safety assessments on C1D1 do not need to be repeated if performed within 3 days of C1D1 at Retreatment Screening Period.

[b] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

Table 2-10: Optional Retreatment Procedural Outline – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 (Retreatment)[b]	Cycle 2 (Retreatment) and beyond (4 weeks ± 3 days)[b]	**Notes:** Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	**D1**	**D1**	
Informed Consent	X			Participants must be re-consented for retreatment.
Eligibility Assessment	X	X		See Section 5.1.6.
Safety Assessments				
Targeted PE, Weight, and Vital Signs	X	X	X	Weight, BP, HR, and temperature prior to treatment. Weight can be assessed up to 24 hours prior to dosing.
ECOG Performance Status	X	X	X	To be performed prior to treatment. See Appendix 5.
Adverse Events Assessment (including SAEs)	Continuously			Record at each visit. Collect continuously throughout the Retreatment Period. See Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously			Record at each visit.
Laboratory Tests				
Clinical Laboratory Testing	X	X	X	Must be performed within 72 hrs prior to dosing. Retreatment C1D1 labs do not need to be repeated if performed in the initial Follow-up Period and within 72 hours prior to retreatment C1D1 dosing. See Table 9.4.4-1 for clinical safety laboratory assessments.
Pregnancy Test WOCBP	X	X	X	Serum or urine pregnancy test must be performed within 72 hours before each dose or at least every 4 weeks (± 1 week) regardless of dosing schedule in cases of dose delays.

Table 2-10: Optional Retreatment Procedural Outline – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 (Retreatment)[b]	Cycle 2 (Retreatment) and beyond (4 weeks ± 3 days)[b]	**Notes:** Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	**D1**	**D1**	
Efficacy Assessments				
Body Imaging	X		See note	Contrast enhanced CT of Chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease should be performed at every 12 weeks (±7 days) from BICR confirmed initial disease progression (starting from date of scan). Tumor assessment schedule should be maintained regardless of dose delays. Scans do not need to be submitted to BICR. Subsequent PD during the Retreatment Period will be per investigator's assessment. Treatment beyond second progression is not allowed. Participants without Investigator-assessed distant metastases must continue tumor scans during the Retreatment Period until metastasis is assessed by the Investigator. Use same imaging method used at screening. All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.1.2 for additional details.
Brain Imaging	X		See note	To be performed as clinically indicated for suspicion of disease. Scans do not need to be submitted to BICR. Subsequent PD during the Retreatment Period will be per investigator's assessment. Treatment beyond second progression is not allowed. See Section 9.1.1.2 for additional details.

Table 2-10: Optional Retreatment Procedural Outline – Arm B (Nivolumab Q4W) (CA20973L)

Procedure	Screening for Retreatment[a]	Cycle 1 (Retreatment)[b]	Cycle 2 (Retreatment) and beyond (4 weeks ± 3 days)[b]	**Notes:** Screening visit may occur on same day as C1D1 retreatment visit
	-28 Days	**D1**	**D1**	
Study Treatment				Participants who enter the Follow-up Period with ongoing disease control (CR, PR, or SD) and without a history of treatment beyond progression, may receive retreatment in Arm B upon BICR confirmed disease progression. Retreatment Period will last up to 12 months with each treatment cycle lasting 4 weeks.
Nivolumab Q4W		X	X	Nivolumab 480 mg administered on D1 of each cycle. See Section 7.1.1.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BP, blood pressure; C, cycle; CR, complete response; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; HR, heart rate; MRI, magnetic resonance imaging; PD, progressive disease; PE, physical examination; PR, partial response; Q4W, every 4 weeks; SAE, serious adverse event; SD, stable disease; WOCBP, women of childbearing potential.

[a] Safety assessments on C1D1 do not need to be repeated if performed within 3 days of C1D1 at Retreatment Screening Period.

[b] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

3 INTRODUCTION

CA20973L is a phase 3, randomized, open label study to compare nivolumab plus concurrent chemoradiotherapy (CCRT) followed by nivolumab plus ipilimumab or nivolumab alone versus CCRT followed by durvalumab in previously untreated locally advanced non-small cell lung cancer (LA NSCLC).

Immunotherapeutic approaches have recently demonstrated clinical efficacy in several cancer types, including NSCLC.[1] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response (see Section 3.2.2.2 and Section 3.2.3 for clinical background on nivolumab and nivolumab plus ipilimumab combination).

Durvalumab is a human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass that inhibits binding of PD-L1 (B7-H1, CD274) to PD-1 (CD279) and CD80 (B7-1). In the phase 3 PACIFIC trial, durvalumab was compared with placebo as maintenance therapy in patients with stage III NSCLC that did not progress after CCRT. Durvalumab significantly prolonged PFS (median 17.2 months vs 5.6 months, HR 0.51; 95% CI, 0.41 to 0.63), and OS (HR 0.68; 99.73% CI, 0.47 to 0.997, P=0.0025).[2] Updated analyses at 48 months further observed an estimated PFS and OS rate of 35.3% and 49.6%, respectively.[3]

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen-presenting cell (APCs), with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

The CA20973L study will allow for direct comparison of novel therapeutic strategy: CCRT with concurrent programmed cell death protein-1 /programmed death-ligand 1 (PD-1/PD-L1) blockade followed by PD-1/PD-L1 blockade with or without CTLA-4 blockade, compared with PD-1/PD-L1 blockade alone after CCRT, as measured by PFS, OS, and other clinical endpoints in previously untreated LA NSCLC.

3.1 Study Rationale

Adding anti PD-1 concurrently to CCRT is hypothesized to improve anti-tumor activity (see Section 5.4.2). In the PACIFIC trial, durvalumab was given after the completion of CCRT. In subgroup analyses, more pronounced improvement in median PFS and OS was seen in participants randomized within 14 days of the last radiation dose compared to participants randomized later, suggesting that initiating PD-1/PD-L1 blockade closer to CCRT may be beneficial.[4] In a mouse model, different combination schedules were assessed. It was observed that initiating PD-1/PD-L1 blockade during radiotherapy led to longer survival times, whereas starting PD-1/PD-L1 blockade 7 days after the completion of radiotherapy yielded similar survival results when compared with radiotherapy alone, which might be due to an acute increase in PD-L1 expression on tumor cells during radiotherapy.[5] Ineffective PD-1/PD-L1 blockade when given in a delayed manner might be explained by the deletion or anergy of tumor-reactive CD8+ cells. In a phase 2 trial (NICOLAS), nivolumab is given concurrently with chemoradiation in locally advanced NSCLC. Preliminary data (see Section 3.2.4) suggested this approach is feasible and safe. [6] Another phase 2 trial combining atezolizumab concurrently with chemoradiation in locally advanced NSCLC showed similar findings.[7]

Furthermore, in the Maintenance Period following CCRT, combining immunotherapeutic agents with different mechanisms of action offers the possibility of a synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation (see Section 3.2.3 and Section 3.2.4 for clinical experience). Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. Available evidence also indicates that incorporating ipilimumab into radiotherapy-based strategy holds promise as, besides abscopal effect, durable response has been observed with ipilimumab in the context of palliative radiotherapy in treating metastatic, refractory NSCLC (see Section 5.4.3).

The current study aims to demonstrate that incorporation of nivolumab to definitive CCRT followed by nivolumab with/without ipilimumab will be efficacious in participants with newly diagnosed untreated LA NSCLC, compared with CCRT followed by durvalumab. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, [redacted] and changes in patient-reported outcomes for quality of life assessments. The safety and efficacy of ipilimumab added to nivolumab maintenance therapy will be characterized descriptively.

3.1.1 Research Hypothesis

CCRT with concurrent nivolumab followed by nivolumab plus ipilimumab will improve PFS and OS in previously untreated LA NSCLC compared with CCRT followed by durvalumab.

3.2 Background

3.2.1 Epidemiology/Indication

Lung cancer has been the most common cancer in the world for several decades. There were estimated to be 1.8 million new cases in 2012 (12.9% of the total). Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total).[8]

Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC was definitive chemoradiation. A meta-analysis of concurrent chemoradiotherapy versus sequential chemoradiotherapy showed better outcomes with concurrent therapy.[9] With improvements such as in staging by using PET and in radiation technologies, 5-year overall survival (OS) was reported up to 30-35%.[10]

Attempts to improve OS include radiotherapy dose escalation/acceleration; new chemotherapy combinations, addition of biological agents, targeted agents, and cancer vaccines to standard regimens. Technical radiotherapy modifications have also been explored. However, none of these efforts has led to an improvement in OS thus far, except for acceleration of radiotherapy in the non-concurrent setting.[11] Recently, durvalumab, an anti-PD-L1 agent, showed an improvement in median PFS, as well as OS in maintenance after CCRT.[2] It is becoming the new standard of care. However, the majority of patients still experienced disease progression or death during the first two years of therapy (18-month PFS rate of 44.2%), and only 57% of patients were alive at 3 years.[4,12] As this stage of disease is potentially curable, new treatment strategies are needed.

3.2.2 Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[13,14,15] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the TCR. [16] Collectively, these signals govern the balance between T-cell activation and tolerance.

3.2.2.1 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[17] Ipilimumab is a fully human

monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.2.2 Nivolumab Mechanism of Action

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA. [18] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ and Bcl-xL. PD-1 expression also has been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[19] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTL-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/NPAN02).[20]

3.2.2.3 Clinical Experience with Nivolumab in NSCLC

Approval of nivolumab in advanced NSCLC was based on 2 phase 3 trials (CheckMate 017 and CheckMate 057) which demonstrated survival benefit over docetaxel across histologies in previously treated patients.

The approval in squamous NSCLC was based on the results of CA209017, a randomized trial of nivolumab versus docetaxel. The median OS for patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, although there was a trend toward better efficacy for those with PD-L1 expressing tumors. A single-arm trial (CA209063) of 117 patients with metastatic squamous NSCLC with progression after platinum-based chemotherapy and at least 1 additional systemic regimen showed a 15% objective response rate (ORR); 59% of participants with a response had response durations of 6 months or longer.[21]

The approval of nivolumab for the treatment of non-squamous NSCLC is based on a second phase 3 study, CA209057, which met its primary endpoint of superior OS of nivolumab versus docetaxel in patients with previously treated non-squamous NSCLC at a preplanned interim analysis.

Patients in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). The safety profile was also more favorable for nivolumab vs docetaxel.[22]

Although the first-line CA209026 trial did not demonstrate that single agent nivolumab provided superior efficacy over platinum doublet chemotherapy, the efficacy of nivolumab was similar to that of chemotherapy in this first line patient population.[23]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the Investigator Brochure and local package insert.

3.2.3 Clinical Experience with Nivolumab plus Ipilimumab Combination Therapy

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules across various tumor types.

CA209012 was a multi-arm phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced non-small cell lung cancer (NSCLC), as either monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of objective response rate (ORR) per RECIST 1.1 and 24-week progression-free survival (PFS). Participants were assigned to receive nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W (n=38), nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W (n=39) and nivolumab 3 mg/kg Q2W (n=52). The confirmed ORR was 47% (N3 Q2W + I1 Q12W), 39% (N3 Q2W + I1 Q6W) and 23% (N3 Q2W).

The rate of treatment-related adverse events (AEs) in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3/4 adverse events were 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in patients administered the optimized dosing schedule (3 mg/kg of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related Grade 3 and Grade 4 AEs per category.

Efficacy and safety profiles were further described with nivolumab combined with ipilimumab in the ongoing phase 3 CheckMate 227 study which enrolled patients with stage IV or recurrent NSCLC who were not previously treated. Those with a level of tumor PD-L1 expression of at least 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy. Those with a tumor PD-L1 expression level of less than 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy. Co-primary endpoints were PFS in patients with a TMB ≥ 10 mutations/Mb using the FoundationOne CDx assay, and OS in patients with PD-L1 expression ≥ 1%.

In the PFS analysis of patients with high tumor mutational burden (≥ 10 mutations/Mb), PFS was significantly longer in the group treated by nivolumab plus ipilimumab compared with chemotherapy, demonstrating a median PFS of 7.2 months vs 5.5 months, respectively (HR = 0.58; 97.5% CI: 0.41, 0.81, P < 0.001), and was numerically better than that of nivolumab alone (HR = 0.75; 95% CI: 0.53, 1.07).[24]

In the OS analysis in patients with PD-L1 expression ≥1%, the combination of nivolumab plus ipilimumab significantly prolonged survival compared with chemotherapy, reducing the risk of death by 21% (HR = 0.79; 95% CI: 0.65, 0.96).[25] The median duration of OS was 17.1 months (95% CI: 15.0, 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI: 12.7, 16.7) with chemotherapy (P = 0.007), and 2-year survival rates were 40.0% and 32.8%, respectively. The ORR was 35.9% (95% CI: 31.1, 40.8) with nivolumab plus ipilimumab (5.8% of patients had a complete response) versus 30.0% (95% CI: 25.5, 34.7) with chemotherapy (1.8% of patients had a complete response). The median duration of response was 23.2 months and 6.2 months, respectively. The response rate and duration of response for nivolumab monotherapy was 27.5% and 15.5 months, respectively, showing the added anti-tumor activity of the nivolumab plus ipilimumab combination. An OS benefit was also observed in patients with PD-L1 expression less than 1%, with a median survival duration of 17.2 months (95% CI: 12.8, 22.0) with nivolumab plus ipilimumab and 12.2 months (95% CI: 9.2, 14.3) with chemotherapy. Across trial participants (irrespective of PD-L1 expression), the median duration of OS was 17.1 months (95% CI: 15.2, 19.9) with nivolumab plus ipilimumab and 13.9 months (95% CI: 12.2, 15.1) with chemotherapy. The percentage of patients with grade 3 or 4 treatment-related AE in the overall population was 32.8% with nivolumab plus ipilimumab and 36.0% with chemotherapy. The overall safety profile was consistent with previously reported data, with no new safety signals.

Overall, the results from the CheckMate 227 trial demonstrate the potential of the nivolumab plus ipilimumab combination to improve treatment outcomes in patients with NSCLC, irrespective of PD-L1 expression.

The approval of nivolumab plus ipilimumab plus 2 cycles of chemotherapy in first-line NSCLC was based on the results of CA2099LA, a randomized trial of nivolumab 360 mg every 3 weeks (Q3W) plus ipilimumab 1 mg/kg Q6W plus 2 cycles of chemotherapy (treatment arm) vs 4 cycles of chemotherapy with optional pemetrexed as maintenance (control arm) for non-squamous histology. This trial met its primary endpoint of OS at the interim analysis with a minimum follow up of 8.1 months (HR = 0.69, 96.71% CI: 0.55, 0.87; p = 0.0006). After a minimum follow up of 12.7 months, median OS was 15.6 months in the treatment arm, and 10.9 months in the control arm, yielding a HR of 0.66 (95% CI: 0.55, 0.80) with OS benefit also observed across prespecified subgroups. A PFS advantage was demonstrated in the treatment arm vs control arm with a median of 6.7 vs 5.0 months (HR = 0.68; 95% CI: 0.57, 0.82), respectively. A significant improvement in ORR was also observed with a response rate of 38% in the treatment arm vs 25% in the control arm (Odds Ratio = 1.9, 95% CI: 1.4, 2.6). The safety profile remains consistent with previous findings with no new toxicity signals and Grade 3/4 treatment-related AEs rates being 47% in the treatment arm and 38% in the control arm.[26]

3.2.4 Clinical Experience with Nivolumab and CCRT

The safety, tolerability, and feasibility of administering nivolumab concurrently with CCRT in patients with stage III locally advanced NSCLC is supported by data from the Phase 2 NICOLAS trial.[27] In the NICOLAS trial, participants received 3 cycles of platinum-based chemotherapy (cisplatin or carboplatin combined with etoposide, pemetrexed or vinorelbine) concurrently with radiotherapy (66 Gy/ 33 fractions) and nivolumab (360 mg every 3 weeks). Radiotherapy techniques during CCRT included VMAT, IMRT or 3DRT, with a mean lung dose of < 20 Gy. Following CCRT, participants received nivolumab maintenance therapy for up to 1 year at a dose of 480 mg every 4 weeks.

The primary endpoint in the NICOLAS trial was pneumonitis-free rate (Grade ≥ 3) observed at any time during 6 months post-radiotherapy. One formal interim safety analysis was performed when the first 21 participants reached 3 months post-radiotherapy follow-up. Success at the interim analysis would be declared if there were zero Grade ≥ 3 pneumonitis events in the 21 evaluable participants. Otherwise, at the final analysis, at least 33 of the 41 participants would be required to be Grade ≥ 3 pneumonitis-free at 6 months post-radiotherapy to reject the null hypothesis.

At the interim analysis (completed in September 2017), zero Grade ≥ 3 pneumonitis events were observed, demonstrating the safety and tolerability of nivolumab combined with CCRT. By August 2018, 41 evaluable participants reached 6 months post-CCRT follow-up. Thirty-six participants had not experienced Grade ≥ 3 pneumonitis, above the boundary for null hypothesis rejection of ≥ 33 participants remaining event-free. These results provide additional support for the interim analysis conclusion that nivolumab + CCRT is safe and tolerable.

In this ongoing trial, up to May 2019, data are available for 77 safety-evaluable patients with a median follow-up of 20.9 months. In this safety cohort, 8 Grade 3 pneumonitis events were reported, 7 of which resolved.[28]

Based on the formal interim safety analysis in the first 21 participants, the informal safety verification in the first 41 participants, and the incidence of pneumonitis Grade ≥ 3 in the full safety cohort of 77 participants, NICOLAS study investigators determined that no unexpected AEs or increased safety risk was observed in the trial.

In part 2 of another phase 2 trial (DETERRED) combining atezolizumab concurrently with chemoradiation in locally advanced NSCLC also suggested that PD-L1 blockade given concurrently with chemoradiation was feasible and safe.[7] The chemotherapy component consisted of weekly low dose carboplatin and paclitaxel concurrently with radiotherapy followed by 2 cycles of full dose carboplatin/paclitaxel as consolidation. Of the 30 participants who received at least 1 dose of therapy, 3 participants (10%) reported pneumonitis (two Grade 2 events and one Grade 3 event). The overall toxicity profile of atezolizumab with CCRT followed by consolidation and maintenance atezolizumab was similar to CCRT alone followed by consolidation and maintenance atezolizumab.

In the Keynote 799 study, patients with unresectable, locally advanced, Stage III NSCLC were randomized into two cohorts containing pembrolizumab and chemoradiation given concurrently

with the chemotherapy component consisting of carboplatin/paclitaxel in Cohort A (N = 112) and cisplatin/pemetrexed in Cohort B (N = 73). An ORR of 69.6% (n = 78; 95% CI: 60.2-78.0) in Cohort A and 70.5% (n = 43; 95% CI: 57.4-81.5) in Cohort B was observed with an estimated response duration of ≥ 12 months in most patients with a response. 1-year OS rates in both cohorts were > 80%. Safety results were also consistent with findings in other similar studies. Given a median follow up of 8.3 months in Cohort A and 5.8 months in Cohort B, Grade ≥ 3 pneumonitis occurred in 9 (8.0%) patients in Cohort A, and in 4 (5.5%) patients in Cohort B.[29]

Collectively, the results from the NICOLAS, DETERRED, and Keynote 799 trials support the combination of nivolumab with CCRT in the CA20973L trial.

3.3 Benefit/Risk Assessment

Lung cancer has been the most common cancer in the world for several decades and the most common cause of death from cancer worldwide. Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC has been definitive chemoradiation. CCRT as standard of care has a well-established safety profile. A meta-analysis of concurrent versus sequential chemoradiotherapy showed better outcomes with concurrent therapy.[9]

Durvalumab, an anti-PD-L1 agent, showed an improvement in median PFS and OS as maintenance therapy in patients who did not experience disease progression after CCRT.[2] However, the majority of patients still experienced disease progression or death during the first two years of therapy (18-month PFS rate of 44.2%), and only 57% of patients were alive at 3 years.[4,12] Updated analyses at 48 months further observed a decrease in PFS and OS with an estimated rate of 35.3% and 49.6%, respectively.[3] Therefore, further improvement in cure rate is needed, given this stage of disease is potentially curable. In addition, the PACIFIC trial only included patients in whom disease had not progressed after CCRT. Mitigating the risk of disease progression on or right after CCRT represents another high unmet medical need. Please refer to the approved Product Label for durvalumab for additional information.

Clinical and preclinical data have shown the potential for concurrent administration of anti-PD-1/PD-L1 therapy with CCRT to improve clinical outcomes.[5,12] Safety data from the NICOLAS trial provides evidence for the feasibility of nivolumab 360 mg Q3W given concurrently with CCRT, with no increased safety risk.[6,27,28] Furthermore, clinical evidence from CheckMate 227 supports the potential for the combination of nivolumab and ipilimumab maintenance therapy to further improve the cure rate and overall treatment outcomes for patients with LA NSCLC.[25]

Extensive details on the safety profile of nivolumab and ipilimumab are available in their respective Investigator Brochures and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD

reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms for nivolumab and ipilimumab have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

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

Bristol-Myers Squibb (BMS) has given consideration regarding the benefit/risk of coronavirus disease 2019 (COVID-19) vaccination during participation in BMS clinical trials of nivolumab and ipilimumab. Based on the review of current available data and evidence to date, knowledge of the mechanisms of action of the COVID-19 vaccines and nivolumab or ipilimumab investigation [medicinal] products (IPs/IMPs), a biological or pharmacological interaction occurring between the vaccine and the IPs that would negatively impact the benefit/risk for participants in BMS clinical trials of nivolumab and ipilimumab is not expected; however, data will continue to be reviewed. Therefore, at this time, a COVID-19 vaccine given to participants in this trial is considered a concomitant medication with no interaction.

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

To assure an ongoing favorable risks/benefit assessment for participants, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and efficacy of treatments throughout the conduct of the trial. Furthermore, quality assurance for radiotherapy will be in place to ensure adherence to the radiation plan.

4 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The study objectives and endpoints described below will be evaluated for the following treatment regimens:

- Arm A: Nivolumab + CCRT followed by nivolumab + ipilimumab maintenance
- Arm B: Nivolumab + CCRT followed by nivolumab maintenance
- Arm C: CCRT followed by durvalumab maintenance

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare progression-free survival (PFS) for Arm A vs Arm C	• PFS by RECIST 1.1 per BICR

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Secondary	
To compare OS for Arm A vs Arm C	• OS for Arm A vs Arm C
To evaluate PFS and OS for Arm B vs Arm C and Arm A vs Arm B	• PFS by RECIST 1.1 per BICR for Arm B vs Arm C • OS for Arm B vs Arm C • PFS by RECIST 1.1 per BICR for Arm A vs Arm B • OS for Arm A vs Arm B
To evaluate tumor response for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to BICR assessment	• Objective Response Rate (ORR) by RECIST 1.1 per BICR • Duration of response (DoR) by RECIST 1.1 per BICR • Time to response (TTR) by RECIST 1.1 per BICR
To evaluate PFS and tumor response for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to Investigator assessment of tumor imaging	• PFS by RECIST 1.1 per Investigator assessment • ORR by RECIST 1.1 per Investigator assessment • DoR by RECIST 1.1 per Investigator assessment • TTR by RECIST 1.1 per Investigator assessment
To evaluate time to death or distant metastases (TTDM) for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B according to Investigator assessment of tumor imaging	• TTDM by RECIST 1.1 per Investigator assessment
To assess safety and tolerability of study treatments	• Incidence of AEs, SAEs, and select AEs
To evaluate symptom deterioration for Arm A vs Arm C, Arm B vs Arm C, and Arm A vs Arm B	• Proportion of participants without meaningful symptom deterioration following 48 weeks of maintenance therapy based on NSCLC-SAQ
Exploratory	
To characterize changes in cancer-related symptoms and quality-of-life between treatment arms in participants with untreated LA NSCLC	• FACT-L total and sub-scale scores • NSCLC-SAQ total score and items • EQ-5D-5L VAS and utility index
To evaluate psychometric measurement properties of the LCS sub-scale of FACT-L and NSCLC-SAQ	• Reliability, validity, and responsiveness of the LCS sub-scale of FACT-L and NSCLC-SAQ • Threshold for clinically meaningful change
To evaluate the tolerability of study treatments	• Symptomatic adverse events as measured by the GP5 item of the FACT-L
To evaluate investigator-assessed outcomes on next-line therapies	• PFS on next line therapy (PFS-2) per Investigator assessment

[redacted]

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	
To characterize the pharmacokinetics (PK) of ipilimumab and nivolumab when administered in combination or for nivolumab when administered as monotherapy	• PK parameters
To assess immunogenicity of nivolumab monotherapy and nivolumab and ipilimumab combination therapy	• Incidence of anti-drug antibodies against ipilimumab and nivolumab when administered in combination or against nivolumab when administered as monotherapy
To assess healthcare resource utilization (HCRU) in each treatment arm	• Incidence of HCRU (eg, hospital admissions, number of days, discharge diagnosis, date of visits, etc) as documented in eCRF

Abbreviations: AE, adverse event; BICR, blinded independent central review; [redacted] DoR, duration of response; eCRF, electronic case report form; EQ-5D-5L, 5-level version of the EuroQol Group's EQ-5D; FACT-L, Functional Assessment of Cancer Therapy - Lung; HCRU, healthcare resource utilization; LA NSCLC, locally advanced non-small cell lung cancer; LCS, lung cancer subscale; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; [redacted] PFS, progression-free survival; PFS-2, progression-free survival on next line therapy; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TTDM, time to death or distant metastases; TTR, time to response; VAS, visual analog scale.

4.1 Estimand for Primary Objective

The main estimand corresponding to the primary objective is stratified hazard ratio in PFS by RECIST 1.1 per blinded independent central review (BICR) between nivolumab + CCRT followed by maintenance therapy with nivolumab + ipilimumab (Arm A) vs CCRT followed by maintenance therapy with durvalumab (Arm C) in patients with previously untreated, locally advanced Stage IIIA/IIIB/IIIC NSCLC, irrespective of initiation of subsequent anti-cancer therapy.

The supplemental estimand corresponding to the primary objective is stratified hazard ratio in PFS by RECIST 1.1 per BICR between nivolumab + CCRT followed by maintenance therapy with nivolumab + ipilimumab (Arm A) vs CCRT followed by maintenance therapy with durvalumab (Arm C) in patients with previously untreated, locally advanced Stage IIIA/IIIB/IIIC NSCLC, accounting for initiation of subsequent anti-cancer therapy.

The following tables Table 4.1-1 and Table 4.1-2 list the attributes of the main estimand and supplemental estimand for the primary objective.

Table 4.1-1: Summary of Attributes of the Main Estimand for Primary Objective

Attribute	Definition Details		
Treatment	Nivolumab + CCRT followed by nivolumab + ipilimumab maintenance vs CCRT followed by durvalumab maintenance		
Population	Patients with previously untreated locally advanced Stage IIIA/IIIB/IIIC NSCLC		
Variable	PFS by RECIST 1.1 per BICR, defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1), or death due to any cause, whichever occurs first		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Premature discontinuation of study therapy	Treatment policy strategy	Disregard the intercurrent event and use the time of PD or death irrespective of treatment discontinuation
	Subsequent anti-cancer therapy prior to PD or death	Treatment policy strategy	Disregard the intercurrent event and use the time of PD or death irrespective of initiation of subsequent therapy
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; ICE, intercurrent event; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Table 4.1-2: Summary of Attributes of the Supplemental Estimand for Primary Objective

Attribute	Definition Details		
Treatment	Nivolumab + CCRT followed by nivolumab + ipilimumab maintenance vs CCRT followed by durvalumab maintenance		
Population	Patients with previously untreated locally advanced Stage IIIA/IIIB/IIIC NSCLC		
Variable	PFS by RECIST 1.1 per BICR, defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1), or death due to any cause, whichever occurs first		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Premature discontinuation of study therapy	Treatment policy strategy	Disregard the intercurrent event and use the time of PD or death irrespective of treatment discontinuation
	Subsequent anti-cancer therapy prior to PD or death	Hypothetical strategy	Participants are censored at the last evaluable tumor assessment prior to the start of subsequent anti-cancer therapy
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; ICE, intercurrent event; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

4.2 Estimand for Key Secondary Objective

The main estimands corresponding to the key secondary objectives are stratified hazard ratio in OS between nivolumab + CCRT followed by maintenance therapy with nivolumab + ipilimumab (Arm A) vs CCRT followed by maintenance therapy with durvalumab (Arm C), and nivolumab + CCRT followed by maintenance therapy with nivolumab (Arm B) vs CCRT followed by maintenance therapy with durvalumab (Arm C) in patients with previously untreated locally advanced Stage IIIA/IIIB/IIIC NSCLC.

Table 4.2-1: Summary of Attributes of the Main Estimand for Secondary Objective (Arm A vs Arm C)

Attribute	**Definition Details**		
Treatment	Nivolumab + CCRT followed by nivolumab + ipilimumab maintenance vs CCRT followed by durvalumab maintenance		
Population	Patients with previously untreated locally advanced Stage IIIA/IIIB/IIIC NSCLC		
Variable	OS, defined as the time between the date of randomization and the date of death due to any cause		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Premature discontinuation of study therapy	Treatment policy strategy	Disregard the intercurrent event and use the time of death regardless of treatment discontinuation
	Subsequent anti-cancer therapy prior to death	Treatment policy strategy	Disregard the intercurrent event and use the time of death irrespective of subsequent anti-cancer therapy
	Lost to follow-up	While on treatment strategy	Participants are censored at last known alive date
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Abbreviations: CCRT, concurrent chemoradiotherapy; ICE, intercurrent event; NSCLC, non-small cell lung cancer; OS, overall survival.

Table 4.2-2: Summary of Attributes of the Main Estimand for Secondary Objective (Arm B vs Arm C)

Attribute	Definition Details		
Treatment	Nivolumab + CCRT followed by nivolumab maintenance vs CCRT followed by durvalumab maintenance		
Population	Patients with previously untreated locally advanced Stage IIIA/IIIB/IIIC NSCLC		
Variable	OS, defined as the time between the date of randomization and the date of death due to any cause		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Premature discontinuation of study therapy	Treatment policy strategy	Disregard the intercurrent event and use the time of death irrespective of treatment discontinuation
	Subsequent anti-cancer therapy prior to death	Treatment policy strategy	Disregard the intercurrent event and use the time of death irrespective of subsequent anti-cancer therapy
	Lost to follow-up	While on treatment strategy	Participants are censored at last known alive date
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Abbreviations: CCRT, concurrent chemoradiotherapy; ICE, intercurrent event; NSCLC, non-small cell lung cancer; OS, overall survival.

5 STUDY DESIGN

5.1 Overall Design

This is a multicenter, randomized, open-label, Phase 3 study to compare nivolumab plus CCRT followed by nivolumab and ipilimumab combination (Arm A) or nivolumab plus CCRT followed by nivolumab alone (Arm B) with CCRT followed by durvalumab (Arm C) in previously untreated LA NSCLC. The safety and efficacy of ipilimumab added to nivolumab maintenance therapy will also be characterized by evaluating Arm A vs Arm B descriptively.

The study is divided into a Screening Period, a Concurrent Chemoradiotherapy (CCRT) Period, a Recovery Period, a Maintenance Period, and a Long-term Follow-up Period. The treatment period will contain a CCRT Period, a Recovery Period, and a Maintenance Period.

Participants will be randomized (1:1:1) across 3 treatment arms:

- **Arm A**:
  - CCRT Period: Nivolumab (360 mg flat dose IV Q3W) for cycles 1 to 3 + platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - Maintenance Period: Nivolumab (360 mg flat dose IV Q3W) + ipilimumab (1 mg/kg IV Q6W) for up to 12 months

- **Arm B**:
  - CCRT Period: Nivolumab (360 mg flat dose IV Q3W) for cycles 1 to 3 + platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - Maintenance Period: Nivolumab (480 mg flat dose IV Q4W) for up to 12 months
- **Arm C:**
  - CCRT Period: Platinum doublet chemotherapy (IV Q3W) for cycles 1 to 3 + radiotherapy (total dose of 60-66 Gy) for cycles 2 to 3
  - Maintenance Period: Durvalumab (10 mg/kg IV Q2W) for up to 12 months

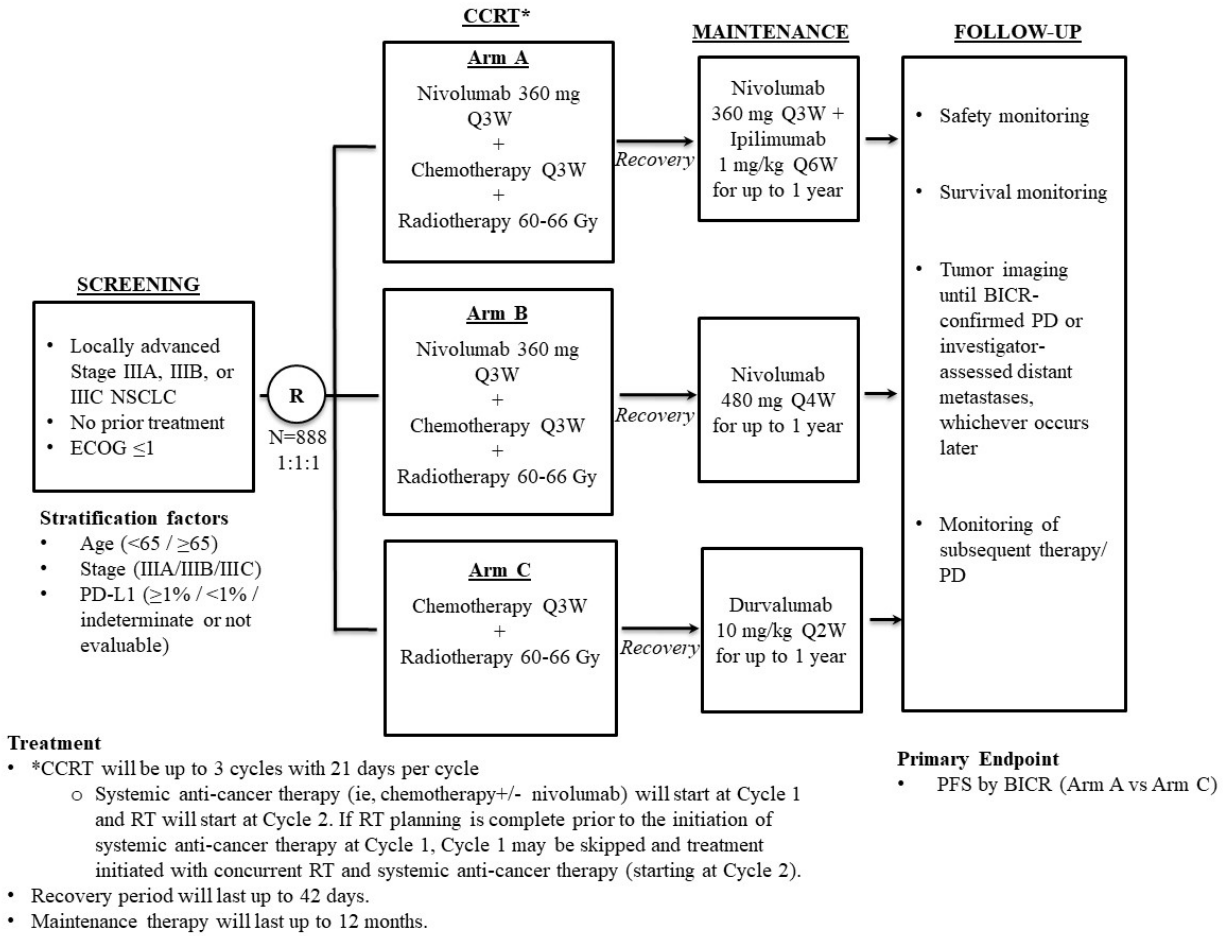
If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT Period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT Period are still to be followed. The Recovery Period will begin after the final dose of radiotherapy and the completion of Cycle 3 procedures as outlined in the Schedule of Activities. An additional cycle of consolidation chemotherapy + nivolumab (Arms A and B) or chemotherapy alone (Arm C) will **not** be administered after the completion of radiotherapy in this situation.

- Randomization will be stratified by:
- Age:
  - < 65 years
  - ≥ 65 years
- Tumor PD-L1 status:
  - ≥ 1%
  - < 1%
  - indeterminate or not evaluable
- Stage (per AJCC 8th edition):
  - IIIA
  - IIIB
  - IIIC

The proportions of participants with indeterminate or not evaluable tumor PD-L1 status will be monitored and reassessed as needed to ensure that the sample size in this stratum is adequate for analysis. Details will be described in the statistical analysis plan.

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

Figure 5.1-1: Study Design Schematic



Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; N, number of participants; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; R, randomize; RT, radiotherapy.

5.1.1 Screening Period

Participants will provide written informed consent (ICF) to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participant's standard care. After signing the ICF, participants will be evaluated for entry criteria during the Screening Period within 28 days before randomization. Re-enrollment after screen failure will be allowed. Tumor imaging during Screening will include whole body PET/CT (including contrast) of the base of the skull through the upper thighs, within 28 days prior to randomization. PET component can be performed within 42 days prior to randomization. A separate contrast enhanced CT of chest, CT or MRI of upper abdomen (including adrenal glands, and full liver), and other suspected sites of disease is required if the CT component of the PET/CT is not of sufficient diagnostic quality for RECIST 1.1 assessments. Imaging of the brain with MRI (with and without contrast) is required of all participants during Screening within 28 days prior to

randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated or based on Investigator discretion.

All participants must have tissue submitted during screening. See Section 6.1 (Inclusion Criteria) and Section 9.8 (Biomarkers) for specifications. Sufficient, recent tumor tissue obtained within 3 months prior to enrollment from a tumor lesion (formalin-fixed, paraffin-embedded block or 5 to 10 unstained slides, obtained from core biopsy, excisional biopsy or surgical specimen) will be submitted to the central laboratory along with an associated pathology report. Fine needle aspiration is unacceptable for submission. In order for the participants to be treated, the sample must be submitted to the central laboratory for the PD-L1 test, and the PD-L1 status must be available to IRT prior to randomization. PD-L1 testing will be performed using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx assay. Participants should not have received any local or systemic anticancer therapy after the date that the submitted tumor tissue was obtained.

Clinical TNM staging should be performed per major guidelines (eg, ESMO, NCCN). Participants must be evaluated by the site's multidisciplinary team (eg, medical oncologist, surgeon, radiologist) during screening to assess the suitability of the participant for the study.

Except for overt cT4 disease, nodal status N2 or N3 must be proven by biopsy in at least one N2 or N3 node via endobronchial ultrasound (EBUS), mediastinoscopy, or thoracoscopy. In addition, T3N1 status must be proven in at least one N1 node (if lesion amenable or medically feasible) via one of these modalities. See Appendix 8 for summary for recommendations for nodal GTV delineation.

5.1.2 CCRT Period

Participants in all arms will receive CCRT. Participants in Arm A and Arm B will receive the addition of nivolumab concurrently with CCRT; whereas participants in Arm C will receive CCRT alone during the CCRT Period. After randomization, participants must commence systemic study treatments (chemotherapy ± nivolumab) within 7 days.

Chemotherapy consists of up to 3 cycles of platinum-based doublet treatment, administered in 3-week cycles (Cycles 1 to 3). Prior to randomization, the planned chemotherapy regimen, the planned number of cycles of chemotherapy (up to 2 cycles or up to 3 cycles), the planned dose level of chemotherapy at the start of treatment for agents with more than 1 possible dose level per protocol (e.g. carboplatin, paclitaxel), and the radiation modality must be pre-defined and documented in the IRT and medical records by the investigator. Please note that if the actual treatment regimen administered to the participant during the CCRT Period changes from the planned regimen documented in the IRT prior to randomization, the rationale for the change must also be recorded in the case report form (CRF) and documented in the medical record. Participants with tumor of squamous histology will receive etoposide/cisplatin or paclitaxel/carboplatin. Participants with tumor of non-squamous histology will receive either etoposide/cisplatin, paclitaxel/carboplatin, or pemetrexed/cisplatin. If cisplatin cannot be tolerated, cisplatin may be replaced with carboplatin and the rationale must be documented in the CRF and medical record. If pemetrexed cannot be tolerated, pemetrexed may be replaced with etoposide and the rationale must be documented in the CRF and medical record. Recommended dose modification schedule

(Section 7.4.5) should be followed; however, local standards and clinical judgment should be used for individual cases.

Radiotherapy starts on the first day of Cycle 2 of chemotherapy and consists of a target physical dose of 60-66 Gy in 30-33 daily fractions of 2 Gy (typically on a 5 days on/2 days off schedule as appropriate, over 6-7 weeks) by intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), or 3-dimentional RT (3DRT). It is recommended that radiotherapy be administered on the same day and after the completion of systemic anticancer therapy. If logistically infeasible, a window of ± 3 days is permitted. In case the administration of systemic anticancer therapy must be delayed due to toxicity, radiotherapy must start ± 3 days of the start of systemic anticancer therapy in Cycle 2.

If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. An additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy in this situation.

Sites must be equipped and qualified to deliver standard of care radiotherapy concurrent with systemic anticancer therapy. Radiotherapy will be subject to a QA process. This will involve site qualification/credentialization and real time review of radiotherapy plans with real time feedback to sites. Upon completion of radiotherapy, all data must be submitted for final analysis. QA services will be provided by an external vendor who will provide a separate radiotherapy manual to describe detailed radiotherapy requirements and QA processes.

In Arm A and Arm B, nivolumab 360 mg IV Q3W for up to 3 cycles (Cycles 1 to 3) will be given concurrently to chemotherapy or chemoradiotherapy, starting on the first day of each cycle and must be given prior to the administration of chemotherapy. It is also recommended that nivolumab be given prior to radiotherapy on the same day if logistically feasible.

Every effort should be made to continue radiotherapy during the CCRT Period in an uninterrupted manner. In case of severe toxicities, such as high-grade esophagitis necessitating interruption of systemic anticancer therapy, radiotherapy may continue as appropriate provided the investigator believes supportive care will enable the participant to complete this part of therapy without excessive risk. Additional details are included in chemotherapy and radiotherapy toxicity management sections of the protocol (Sections 7.4.5 and 7.6). Compliance will be documented in the eCRF.

Participants who have confirmed disease progression by blinded independent central review (BICR) during the CCRT Period will be discontinued from the treatment and enter the Follow-up Period. However, all study treatment decisions will be based on the investigator's assessment of tumor images. In case of premature discontinuation of CCRT with reasons other than PD, as confirmed by BICR, continuation of the participant into the recovery period may be considered based on discussion with the Medical Monitor and Investigator.

5.1.3 Recovery Period

Recovery Period lasts approximately 3 weeks up to 6 weeks from the end of the CCRT Period (ie, last dose of radiotherapy). For participants who are recovering from toxicities associated with CCRT treatment, the first dose of maintenance immunotherapy may be delayed up to 6 weeks from the end of CCRT (ie, last dose of radiotherapy). If further delay (> 6 weeks) is needed, approval by medical monitor or designee is required to move on to the maintenance period, and this must be documented in the participant's medical record.

Tumor measurement imaging, safety evaluations, and other procedures should be performed approximately 3 weeks following the completion of CCRT (ie, last dose of radiotherapy). Tumor imaging during the Recovery Period will be the first on-treatment scan for the study. Other examinations during the Recovery Period should be performed as close as possible to the anticipated commencement of maintenance immunotherapy.

The maintenance immunotherapy begins when the investigator determines that the participant has recovered from the effects of the combined modality treatment sufficiently. For entry into the Maintenance Period, participants must meet all eligibility criteria detailed in Section 6.1.2.

Participants receiving pemetrexed during the CCRT Period should continue their scheduled folic acid until 21 days after the last dose of pemetrexed or per local standard.

Participants who do not meet any criteria of initiating maintenance immunotherapy should proceed to the Follow-up Period.

5.1.4 Maintenance Period

Maintenance Period lasts for up to 12 months of treatment for Arm A, Arm B, and Arm C. The first dosing in maintenance can be initiated within 2 weeks from the end of CCRT (ie, last dose of radiotherapy) but no less than 18 days from the previous dosing of nivolumab (Arm A and B) and should be given within 3 calendar days from completion of the last visit in the Recovery Period provided eligibility criteria are met.

Maintenance Period of the study consists of multiple treatment cycles with associated evaluations and procedures specified in Table 2-5, Table 2-6, and Table 2-7. One cycle of treatment is defined as 6 weeks for Arm A, as 4 weeks for Arm B, or as 2 weeks for Arm C. Every effort should be made to schedule visits within the protocol-specified windows.

Contrast enhanced CT of chest, CT or MRI of upper abdomen (including adrenal glands, full liver), and other suspected sites of disease should be performed 24 weeks (± 7 days) from randomization, then every 12 weeks (±7 days) during treatment according to Table 2-5, Table 2-6, and Table 2-7. Tumor imaging should be submitted to BICR on an ongoing basis. In the case of PD as assessed by the investigator (per RECIST 1.1), the images and any associated documentation should be submitted to BICR for independent review of progression. Tumor assessment imaging should continue per protocol schedule and be submitted to BICR until progression is confirmed by BICR, regardless of the start of subsequent anticancer therapies. Furthermore, if the PD is assessed as locoregional progression (i.e. still within the thorax) by the Investigator, imaging must continue

according to the protocol schedule until distant metastasis is assessed by the Investigator (per RECIST 1.1). These images do not need to be submitted to BICR for review.

Participants will be treated until Investigator-assessed disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, withdrawal of consent on further treatment, lost to follow-up, BMS decision to terminate the study, or completion of required treatment in the Maintenance Period. Additional assessments may occur when the decision is made to discontinue treatment.

In certain circumstances, participants with PD per RECIST 1.1, but with otherwise stable or improved performance and clinical status, may continue to be treated in the event of a perceived benefit per Investigator; see Section 8.1.6 for treatment beyond progression criteria.

Participants who cannot complete planned maintenance therapy should enter the Follow-up Period.

BMS may request that survival data be collected on all participants on treatment in the CCRT Period, Recovery Period, or Maintenance Period, if applicable. At the time of this request, each participant will be contacted to determine his/her survival status unless the participant has withdrawn consent for all contact.

5.1.5 Follow Up Period

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. [redacted]

Timing for long-term follow-up will be as follows:

Assessments should continue as described in Table 2-8.

Safety Follow up: Participants must be followed for safety for at least 100 days after the last dose of study treatment. Safety Follow-up Visit 1 should occur 30 days from the last dose (± 7 days). If participant delays treatment and later discontinues treatment > 42 days from the last treatment, the Safety Follow-up Visit 1 may be performed at time of discontinuation. Safety Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of study treatment. Both follow-up visits should be conducted in person. If the participant discontinues study treatment for a clinically significant AE, the participant will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

Survival Follow Up: Post the Safety Follow up, all participants will be contacted for survival every 3 months (± 14 days), by visit (if due for tumor assessments) or phone contact by Investigator's discretion. 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 his/her survival status unless the participant has withdrawn consent for all contact. Tumor assessments should be performed as outlined in Table 2-8. Information on the subsequent PD, subsequent anticancer therapy, and outcome must be collected. Subsequent PD assessment takes participant status at the initial PD as re-baseline, is defined per local standard

practice, and may entail radiological PD, clinical PD, or other. In addition, outcome measures will be collected based on Section 9.1.2.

5.1.6 Optional Retreatment during Follow-up Period in Arm A and Arm B

After completing 12 months of Maintenance Period treatment, retreatment is allowed for participants in Arm A and Arm B. Participants must have entered the Follow-up Period with ongoing disease control (CR, PR, or SD) and without history of treatment beyond progression. After BICR-confirmed PD during the Follow-up Period and at the discretion of the investigator, participants will be treated with the same maintenance dose and schedule from randomization. For Arm A, participants may be retreated with only nivolumab, if ipilimumab was not tolerated. Ipilimumab monotherapy is not allowed during retreatment. The maximum duration of retreatment is up to 1 year and retreatment is allowed only one time for both Arm A and Arm B.

Before retreatment,

- participants must not meet dose delay criteria for nivolumab (see Section 7.4.1) or ipilimumab (see Section 7.4.2).
- participants must not have been treated with any anticancer therapy during the Follow-up Period.
- participants must not have clinical conditions that require urgent medical interventions.
- participants must be re-consented before initiation of retreatment.

At retreatment,

- participants must have a baseline tumor assessment within 28 days before the first dose of retreatment.
- participants will have tumor assessments every 12 weeks (± 7 days) from BICR confirmed initial disease progression (starting from date of scan). Scans during the Retreatment Period do not need to be submitted to BICR. The assessment of PD during the Retreatment Period will be per investigator's assessment using RECIST 1.1.
- participants without Investigator-assessed distant metastases must continue tumor imaging during the Retreatment Period until metastasis is assessed by the Investigator.
- participants will follow study procedures outlined in Table 2-9 (Arm A) and in Table 2-10 (Arm B).

Participants who complete or discontinue retreatment must complete assessments for Safety Follow-up Visit 1, Safety Follow-up Visit 2, and Survival Follow-up (see Table 2-8).

5.1.7 Data Monitoring Committee and Other External Committees

5.1.7.1 Data Monitoring Committee

A Data Monitoring Committee has been established to provide oversight of safety and efficacy considerations in protocol CA20973L and to provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for

nivolumab given concurrently with CCRT as well as in combination with ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

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

Additional details concerning DMC oversight are provided in the DMC charter.

5.1.8 Radiotherapy Quality Assurance and Quality Control

A designated vendor will credentialize sites including the use of a mock case prior to enrollment of the first participant at each site. Furthermore, the vendor will perform real-time review of the radiation plan for the first enrolled participant and provide feedback to the site within 3 days. Treatment will not be delayed, but adjustment of radiation plan may be made as a result of quality review. All participants will have their radiation plans and actual delivery reviewed for the purpose of measuring compliance to protocolled radiation prescription. The RT quality assurance (QA) and quality control (QC) data submission requirements and protocol compliance criteria are detailed in the RT QA & QC manual.

5.2 Number of Participants

It is expected that approximately 1400 participants will be screened in order to randomize 888 participants with previously untreated locally advanced NSCLC, assuming a screen failure rate of approximately 40%. Participants will be randomized (1:1:1) into 1 of the 3 treatment arms (Section 5.1).

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last study visit or last survival assessment/confirmation. The total duration of the study is up to 5 years from randomization of the last participant, or until the time of final OS analysis, whichever occurs later.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Study Population and Study Comparator

This study will evaluate the potential for CCRT + nivolumab followed by nivolumab with/without ipilimumab to improve treatment outcomes compared with CCRT followed by durvalumab for participants with previously untreated, locally advanced Stage IIIA, IIIB, or IIIC NSCLC. Participants will be enrolled if their NSCLC is amenable to treatment with definitive CCRT. Participants who are not planned for potential curative surgical resection will be eligible. Please refer to Section 6.1 for detailed eligibility requirements.

Durvalumab, an anti-PD-L1 agent, showed an improvement in median PFS and OS as maintenance therapy in patients who did not experience disease progression after CCRT (PACIFIC trial).[2] CCRT followed by durvalumab is becoming the new standard of care. However, the majority of patients still experienced disease progression or death during the first two years of therapy

(18-month PFS rate of 44.2%), and only 57% of patients were alive at 3 years.[4,12] Updated analyses at 48 months further observed a decrease in PFS and OS with an estimated rate of 35.3% and 49.6%, respectively.[3] Therefore, new treatment strategies are needed, given this stage of disease is potentially curable. In addition, the PACIFIC study only included patients whose disease had not progressed after CCRT. Mitigating the risk of disease progression on or right after CCRT represents another high unmet medical need.

5.4.2 Rationale of Combining Nivolumab with CCRT

Clinical evidence suggests that the combination of checkpoint inhibitors and radiotherapy may be beneficial. In a secondary analysis of KEYNOTE-001, a phase I trial of pembrolizumab, patients who received radiotherapy followed by pembrolizumab experienced significantly longer progression-free survival and overall survival than did those who had not undergone radiotherapy before anti-PD-1 therapy.[30] Mechanistically, radiation, acting as an in-situ tumor vaccine, releases tumor antigens and helps their presentation to dendritic cells, thus, modulating the immune system and helping to mount an immune response against the tumor.[31] Radiation also provides a pro-immunogenic effect on the tumor microenvironment.[32] Consistently, radiotherapy led to PD-L1 upregulation in tumor cells which was observed in a mouse model, as well as in patients.[5,33] This upregulation of PD-L1 was mediated by interferon gamma produced by CD8+ T cell blockade of PD-1/PD-L1, which enhanced the efficacy of radiotherapy.

Similarly, chemotherapy may modulate the tumor/immune system interaction in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells. Consistently, chemotherapy may induce PD-L1 expression, which relates to cancer immunoresistance.[34]

Taken together, combining PD-1/PD-L1 blockade with chemoradiation has the potential to orchestrate multi-dimensional anti-tumor activities and maintain a pro-immunogenic tumor microenvironment, to improve clinical outcomes in untreated stage III NSCLC.

5.4.3 Rationale of Incorporating Ipilimumab into Radiotherapy-based Strategy

Supportive evidence of incorporating ipilimumab into a radiotherapy-based approach mainly comes from the metastatic, refractory, and palliative settings. Abscopal effect (ie, anti-tumor effects that occur outside the radiation field) was first described in 1953[35] and before the advent of immunotherapy. Recently, an anecdotal case of a durable complete abscopal response to palliative radiotherapy and ipilimumab in a patient with metastatic NSCLC was reported.[36] Similar clinical findings continue to accumulate in NSCLC and other tumor types. [37] Data from a prospective phase 2 trial to evaluate radiotherapy and ipilimumab in chemo-refractory metastatic NSCLC indicate an ORR of 18% (7/39) with 2 CR, in addition, 5 patients had SD, leading to a DCR of 31%. At median follow-up of 43 months, median OS was 7.4 months for the entire cohort,

whereas it was 20.4 months for participants who achieved disease control.[38] Thus, incorporating ipilimumab into radiotherapy-based treatment may also improve outcomes in earlier stages of disease (such as, untreated locally advanced NSCLC).

5.4.4 Rationale of Concurrent Scheduling of Nivolumab with CCRT

The optimal schedule for combining checkpoint blockade and chemoradiation is still unknown. In the PACIFIC trial, durvalumab was given after the completion of CCRT. In subgroup analyses, more pronounced improvement in median PFS was seen in patients randomized within 14 days of the last radiation dose than in those randomized later, suggesting that initiating PD-1/PD-L1 blockade closer to CCRT may be beneficial.

In a mouse model, different combination schedules were assessed. It was observed that initiating PD-1/PD-L1 blockade during radiotherapy lead to longer survival times, whereas starting PD-1/PD-L1 blockade 7 days after the completion of radiotherapy yielded similar survival results when compared with radiotherapy alone.[5] This might be due to an acute increase in PD-L1 expression on tumor cells during radiotherapy; ineffective PD-1/PD-L1 blockade when given in a delayed manner might be explained by the deletion or anergy of tumor-reactive CD8+ cells.

Safety and tolerability may be of concern when further intensifying CCRT by adding immunotherapy. Data from the phase 2 NICOLAS study, designed to evaluate the safety and feasibility of nivolumab given concurrently with CCRT, demonstrated that this combination was well tolerated. Results showed no major increase in prohibitive toxicity including pneumonitis.[24]

Two phase 2 trials combining atezolizumab and pembrolizumab, respectively, concurrently with chemoradiation in locally advanced NSCLC also suggested that PD-L1 blockade given concurrently with chemoradiation was feasible and safe.[7,29]

Therefore, concurrent scheduling of nivolumab with CCRT may offer enhanced efficacy with an acceptable toxicity profile.

5.4.5 Rationale of Duration of Maintenance Therapy

Durvalumab, the control treatment in the CA20973L trial, was approved for 1 year of therapy following CCRT and is becoming the new standard of care. Therefore, a 1-year maintenance duration is opted for in all study arms in the CA20973L trial. Nivolumab (with or without ipilimumab) will be administered for a duration of up to 1 year in alignment with the comparator, durvalumab.

5.4.6 Rationale of Backbone CCRT

The standard dose-fractionation of radiation in unresectable stage III NSCLC is 60-66 Gy, given in fractions of 2 Gy once per day over 30-33 days during definitive CCRT.

The ideal concurrent chemotherapy regimen has not been determined. The most common regimens are cisplatin/etoposide and carboplatin/paclitaxel in ASCO endorsed ASTRO recommendation, whereas in ESMO recommendation, cisplatin/etoposide and cisplatin/vinca alkaloid were cited.[39,40]

In the PROCLAIM trial in which pemetrexed/cisplatin was compared with etoposide/cisplatin in the context of concurrent chemoradiation, pemetrexed/cisplatin failed to show an improvement in OS; however, high grade drug related toxicities were less with pemetrexed/cisplatin.[10] In addition, the ongoing phase 2 NICOLAS trial suggested that nivolumab given concurrently with CCRT containing cisplatin/etoposide, cisplatin/vinorelbine, or cisplatin/pemetrexed was well tolerated.[6] A phase 2 trial combining atezolizumab concurrently with chemoradiation with carboplatin/paclitaxel as the chemotherapy component in locally advanced NSCLC also suggested that PD-L1 blockade given concurrently with chemoradiation was feasible and safe.[7] Similar findings were also obtained from a phase 2 trial with pembrolizumab given concurrently with chemoradiation using carboplatin/paclitaxel (Cohort A) or cisplatin/pemetrexed (Cohort B) as the chemotherapy component (Section 3.2.4).[29] Therefore, cisplatin/etoposide, carboplatin/paclitaxel, and cisplatin/pemetrexed have been selected as concurrent chemotherapy options for the CA20973L trial.

Chemotherapy is generally given in 2 to 4 cycles and up to 3 cycles in the phase 2 NICOLAS trial. In the CA20973L trial, systemic therapy (chemotherapy ± nivolumab) will start at Cycle 1 in the CCRT Period and be administered for up to 3 cycles (Cycles 1 to 3). Radiotherapy will start at Cycle 2 and be administered for Cycles 2 to 3. However, if radiotherapy planning is complete prior to the initiation of systemic treatment at Cycle 1 of the CCRT period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic therapy alone, and initiate treatment with radiotherapy concurrently with systemic therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. There is no clinical evidence supporting further consolidation therapy, [41] and as such, an additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy if Cycle 1 is skipped.

5.4.7 Rationale for Open-Label Design

Immune related toxicities require early recognition and prompt intervention with special management algorithms. Furthermore, PFS and other key tumor response-based endpoints will be assessed by BICR and OS assessment is an objective. Therefore, an open-label design is not expected to introduce bias in this trial.

5.5 Justification for Dose

5.5.1 Justification for Dosing Regimen of Nivolumab

Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[42,43] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive

characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to patients over a wide body weight range (34-180 kg) across tumor types.

Extensive exposure-response (E-R) analyses of multiple PK measures (maximum serum concentration at Day 1, average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade ≥ 3, and immune-mediated AEs (IMAEs) Grade ≥ 2 are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

5.5.2 Justification for Dosing Regimen of Nivolumab plus Ipilimumab

The phase 2 CA209568 study had a safety lead-in phase which evaluated the safe dosing level of nivolumab and ipilimumab plus platinum-based doublet chemotherapy, which is applied in the CA2099LA treatment arm. In CA209568, participants received nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks combined with 2 cycles of platinum-based chemotherapy, followed by nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks until progression or unacceptable toxicity.

The safety lead-in phase of CA209568 treated 36 participants with a minimum follow-up of 11 weeks (longest follow-up of 9 months, median follow-up of 4.7 months). There was 1 case of dose limiting toxicities (DLTs) as defined by hepatic enzyme elevation. No safety concerns were observed with ongoing monitoring (DBL: July, 2018). In August 2017, the independent DMC recommended to initiate CA2099LA based of the evaluation of safety data from study CA209568, where the same dosing regimen was investigated.

Moreover, and in addition to the regular monitoring of the CA2099LA study, the independent DMC had an early review of the safety data after 15 patients were treated with nivolumab and ipilimumab combined with platinum-based doublet chemotherapy with at least 9 weeks of follow-

up. As planned in the CA2099LA DMC Charter, the independent DMC reviewed the safety data during the first safety review meeting in May 2018 and recommended the study to continue with no modification. As of March 2019, 361 patients were randomized in the nivolumab plus ipilimumab treatment arm (with 2 cycles of histology-based platinum doublet chemotherapy) in the CA2099LA study.

In CA209568 and CA2099LA trials, nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks combined with 2 cycles of platinum-based chemotherapy, which was followed by nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks, has been tolerated. Therefore, the CA20973L study using this same IO combination (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W) without chemotherapy should have a less toxic profile and thus should be tolerated. Additionally, safety will be regularly monitored by independent DMC review throughout the CA20973L trial.

6 STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1 Inclusion Criteria

6.1.1 Inclusion Criteria for CCRT

1) Signed Written Informed Consent

a) Participants or legally acceptable representatives (LAR, see Appendix 2) (where acceptable per local guidelines) 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 participant care

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

2) Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (See Appendix 5)

b) Locally advanced stage IIIA, IIIB, or IIIC (T1-2 N2-3 M0, T3 N1-3 M0, or T4 N0-3 M0) pathologically confirmed (including cytology) NSCLC, according to 8th TNM classification,[44] that is amenable to definitive CCRT. Participants who are not planned for potential curative surgical resection are eligible, except for those foregoing surgery due to clinical contraindication for general anesthesia/surgery. Participants must be evaluated by the site's multidisciplinary team (eg, medical oncologist, surgeon, radiologist) during screening to assess the suitability of the participant for the study.

i) Overt cT4 disease. Vertebral invasive disease must not extend into the spinal canal. OR

ii) Nodal status N2 or N3 must be proven (by biopsy in at least one N2 or N3 node, via EBUS, mediastinoscopy, or thoracoscopy) OR

iii) Nodal status N1 must be proven by biopsy in at least one N1 node via EBUS, mediastinoscopy, or thoracoscopy for T3 disease, unless lesion unamenable or medically infeasible (must be documented in medical record).

Note: fine needle aspiration/cytology is acceptable for diagnosis and staging purposes.

c) Newly diagnosed and treatment-naïve, with no prior local or systemic anticancer therapy given as primary therapy for locally advanced disease

d) Measurable disease per RECIST 1.1 criteria

e) All participants must have tissue submitted to a central laboratory during screening. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 5 to 10 unstained tumor tissue sections, obtained within 3 months prior to enrollment, with an associated pathology report, must be submitted to the central laboratory for inclusion. Biopsy should be excisional, core needle or surgical specimen. Fine needle aspiration is unacceptable for submission. The central laboratory must provide IRT with PD-L1 status prior to randomization. PD-L1 testing will be performed using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx assay.

3) Age and Reproductive Status

a) Males and females, ≥ 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) at screening and within 24 hours prior to the start of study treatment.

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

ii) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment and for 5 months post-treatment completion, or according to approved local Product label requirements for individual chemotherapy agents, whichever is longer. Women should use an adequate method(s) of contraception as indicated in Appendix 4

i) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP with documented proof that they are not of childbearing potential

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months post-treatment completion, or according to approved local product label requirements for individual chemotherapy agents, whichever is longer, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

Note: Women who are not of childbearing potential are exempt from contraceptive requirements

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and 7 months post-treatment completion, or according to approved local Product label requirements for individual chemotherapy agents, whichever is longer. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study treatment to a developing fetus.

i) The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

6.1.2 Inclusion Criteria for Maintenance Treatment

4) For entry into maintenance therapy, the following criteria MUST be met:

a) **Note: Inclusion criteria 4 a) was removed as per Protocol Amendment 02.** Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix 5)

b) No BICR-confirmed progressive disease per RECIST 1.1 during or after CCRT

c) No current or prior use of immunosuppressive medication within 14 days before the first dose of maintenance immunotherapy, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of daily prednisone equivalent. Systemic steroid administration required as prophylaxis against or to manage toxicities arising from CCRT is allowed

d) Any toxicity from CCRT should resolve to Grade 1 or baseline (except for Grade 2 fatigue, esophagitis, or alopecia). Participants with irreversible, well controlled, or recovering from toxicity that is not reasonably expected to be exacerbated by study treatment may be included after consultation with the BMS medical monitor. Participants with myelosuppression may be allowed to proceed with maintenance therapy at the investigator's discretion

e) Participants in Arm A and Arm B that received nivolumab should **NOT** meet discontinuation criteria for immunotherapy (Section 8.1.1)

6.2 Exclusion Criteria

6.2.1 Exclusion Criteria for CCRT

1) Medical Conditions

a) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study treatment administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis)

b) Active infection requiring systemic therapy within 14 days prior to randomization

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

d) 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

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

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

g) Presence of pleural/pericardial effusion on CT scan and/or X-ray, unless it is not cytologically positive nor exudative via pleuracentesis. Effusions that are too small to be tapped safely are acceptable

h) Participants with EGFR mutation regardless of mutation type are excluded. Non-squamous tumor with unknown EGFR mutation status must be tested for EGFR mutation (PCR-based test should be used).

i) Known ALK translocation and/or ROS1 rearrangement

j) **Note: Exclusion criteria 1 j) was removed as per revised protocol 01**: Clinical evidence of hearing loss

k) **Note: Exclusion criteria 1 k) was removed as per revised protocol 01**: ≥ Grade 2 peripheral neuropathy

l) History of organ or tissue transplant that requires systemic use of immune suppressive agents

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

n) Previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening. Symptoms must have resolved and based on investigator assessment in consultation with the medical monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment (see Section 6.4.1).

2) Prior/Concomitant Therapy

a) Prior thoracic radiotherapy. Exceptions are prior radiotherapies involving the chest for clinical conditions other than lung cancers (eg, breast cancer) of which the radiation field does not overlap with that of the disease under study AND does not have FDG uptake at the previously irradiated area of the lung per the PET scan performed during screening. All other prior radiotherapy is allowed and must be completed at least 30 days prior to study treatment with residual toxicities resolved prior to study enrollment.

b) Use of an investigational agent or an investigational device within 28 days before administration of first dose of study treatment.

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

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

e) Pancoast tumor or other situations with surgery as part of management plan.

f) Radiation plan is not likely to comply with lung V20 <35% (ideally <30%)

i) **Note: Exclusion criteria 2 f) i was removed as per revised protocol 01**: Mean lung dose <20 Gy and/or V20<35%, AND V5≤60%

ii) **Note: Exclusion criteria 2 f) ii was removed as per revised protocol 01:** Mean esophagus dose <34Gy

iii) **Note: Exclusion criteria 2 f) iii was removed as per revised protocol 01:** Mean heart dose <15Gy

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

3) Physical and Laboratory Test Findings

a) WBC < 2000/µL

b) Neutrophils < 1500/µL

c) Platelets < 100 x 10^3/µL

d) Hemoglobin < 9.0 g/dL

Note: May not transfuse within 14 days of randomization to meet eligibility criteria 3)a, 3)b, 3)c, and 3)d.

e) Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula) for participants receiving carboplatin and ≥60 mL/min for participants receiving cisplatin

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

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

f) AST/ALT > 3.0 x ULN

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

h) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative)

i) Inadequate pulmonary function defined as forced expiratory volume in 1 second (FEV1) ≤ 50% of predicted normal volume and/or carbon monoxide lung diffusing capacity (DLCO) ≤ 40% of predicted normal value

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study treatment components

b) History of severe hypersensitivity reaction to any monoclonal antibody

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.

Note: The approved local Product Label requirements for the individual chemotherapy drugs in this trial must also be followed when determining participant eligibility.

6.2.2 Exclusion Criteria for Maintenance

1) For entry into maintenance therapy, any of the following criteria MUST NOT be met:

a) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study treatment administration or interfere with the interpretation of safety results

2) Physical and Laboratory Test Findings

a) **Criteria 7 a) was removed from revised protocol 01:** WBC < 2000/μL

b) **Criteria 7 b) was removed from revised protocol 01:** Neutrophils < 1500/μL

c) **Criteria 7 c) was removed from revised protocol 01:** Platelets < 100 x 10^3/μL

d) **Criteria 7 d) was removed from revised protocol 01:** Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula)

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

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

f) AST/ALT > 3.0 x ULN

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

If a delay of > 6 weeks is needed in the recovery period, approval by medical monitor or designee is required to move on to the maintenance period, and this must be documented in the participant's medical record.

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

During the CCRT Period, esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Participants should be advised to avoid alcoholic, acidic, or spicy foods or beverages.

6.4 Screen Failures

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

6.4.1 Retesting During Screening Period

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

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

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

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

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

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

7 TREATMENT

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

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

- Ipilimumab Solution for Injection
- Nivolumab Solution for Injection
- Durvalumab Solution for Injection
- Cisplatin Solution for Infusion
- Etoposide Concentrate for Solution for Injection
- Carboplatin Solution for Injection
- Pemetrexed Powder for Concentrate for Solution for Infusion
- Paclitaxel Solution for Infusion

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. **Note:** Radiotherapy administered in this study is **NOT** considered study treatment.

Table 7-1: Study treatments for CA20973L

Product Description / Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label	Vial (one or more vials per carton)	Store at 2 - 8 C. Protect from light and freezing.
Ipilimumab Solution for Injection[a]	50 mg (5 mg/mL)	IP	Open-label	Vial (one or more vials per carton)	Store at 2 - 8 C. Protect from light and freezing.
Nivolumab Solution for Injection[b]	100 mg (10 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Store at 2 - 8 C. Protect from light and freezing.
Cisplatin Solution for Infusion[c]	100 mg/vial (1 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Product should be stored as per market product conditions
Etoposide Concentrate for Solution for Injection[c]	100 mg/vial (20 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Product should be stored as per market product conditions
Durvalumab Solution for Injection[c]	500 mg/vial (50 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Product should be stored as per market product conditions
Carboplatin Solution for Injection[c]	450 mg/vial (10 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Product should be stored as per market product conditions
Pemetrexed Powder for Concentrate for Solution for Infusion[c]	500 mg/vial	IP	Open-label	Vial (one or more vials per carton)	Product should be stored as per market product conditions
Paclitaxel Solution for Infusion[c]	100 mg/vial (6 mg/mL)	IP	Open-label	Vial (one or more vials per carton)	Product should be stored as per market product conditions

Abbreviations: IP, investigational product; SmPC, Summary of Product Characteristics.

[a] 50 mg ipilimumab vial will be available starting Q3 2022 and may be used in this study.

[b] May be labeled as either “BMS-936558-01” or “Nivolumab”.

[c] 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. The approved local product label (including package insert, SmPC, or equivalent), or local standards for preparing and administering these agents may be used, as long as there is no change in the treatment dose or administrative schedule, as specified in the protocol.

7.1 Treatments Administered

Table 7.1-1: Selection and Timing of Dose

Study Treatment[a]	Unit Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	• 360 mg (Arms A and B) • 480 mg (Arm B only)	• Q3W (in CCRT Period for Arms A and B; in Maintenance Period for Arm A) • Q4W (in Maintenance Period for Arm B)	IV
Cisplatin[b] (+ etoposide)	80 mg/m^2	D1 Q3W for up to 3 cycles in CCRT Period	IV
Etoposide[c]	100 mg/m^2	D1 to D3 Q3W for up to 3 cycles in CCRT Period	IV
Cisplatin[b] (+ pemetrexed)	75 mg/m^2	D1 Q3W for up to 3 cycles in CCRT Period	IV
Pemetrexed[c]	500 mg/m^2	D1 Q3W for up to 3 cycles in CCRT Period	IV
Carboplatin (+ etoposide or pemetrexed)	AUC 5	D1 Q3W for up to 3 cycles in CCRT Period	IV
Carboplatin (+ paclitaxel)	a) AUC 5 or 6 b) AUC 2	a) D1 Cycle 1 for 1 cycle in CCRT Period b) D1, D8, D15 for Cycle 2 and Cycle 3 in CCRT Period	IV
Paclitaxel	a) 175 or 200 mg/m^2 b) 45 or 50 mg/m^2	a) D1 Cycle 1 for 1 cycle in CCRT Period b) D1, D8, D15 for Cycle 2 and Cycle 3 in CCRT Period	IV
Ipilimumab	1 mg/kg	Q6W (maintenance in Arm A)	IV
Durvalumab	10 mg/kg	Q2W (Maintenance in Arm C)	IV

Abbreviations: AUC, area under the concentration-time curve; CCRT, concurrent chemoradiotherapy; D, day; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

[a] If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. An additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy in this situation.

[b] If cisplatin cannot be used, it can be replaced by carboplatin.

[c] If pemetrexed cannot be used, it can be replaced by etoposide.

Study agent(s) should be administered in an area with access to resuscitation equipment. All participants should begin study treatment within 7 calendar days of randomization. Information on drug preparation, infusion techniques, and materials required for the infusions are described in Pharmacy Manual.

7.1.1 Nivolumab Dosing

In Arm A and Arm B during CCRT Period, participants should receive nivolumab at a dose of 360 mg over an approximately 30 (± 5) minute IV infusion on Day 1 of each treatment cycle up to 3 cycles and prior to the administration of chemotherapy. If needed, flush the IV line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Participants may be dosed Q3W ± 3 days. See Section 7.4.5 for timing of chemotherapy dosing in case of dose delay of nivolumab. Participants may be dosed no less than 18 days from the previous dose of nivolumab during Q3W cycles. See Section 7.1.5 for option to skip cycle 1 of nivolumab + chemotherapy alone if RT planning is completed prior to the first dose at Cycle 1.

In Arm A Maintenance Period, participants should receive nivolumab at a dose of 360 mg over an approximately 30 (± 5) minute infusion followed by ipilimumab at a dose of 1 mg/kg over an approximately 30 (± 5) minute infusion on Day 1 of every cycle (Q6W cycles). In addition, nivolumab will be administered on Day 22 of every cycle, at a dose of 360 mg over an approximately 30 (± 5) minute infusion. Treatment will continue until confirmed progression, unacceptable toxicity, withdrawal of consent, completion of approximately 12 months of treatment, or the study ends, whichever occurs first. Participants may be dosed Q3W ± 3 days for nivolumab. When study treatments nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred.

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Participants may be dosed no less than 18 days from the previous dose of nivolumab during Q3W cycles. When dose is delayed, see Section 7.4.4 for rules of rescheduling. Premedications are not recommended for the first dose of nivolumab.

In Arm B Maintenance Period, participants should receive nivolumab at a dose of 480 mg over an approximately 30 (± 5) minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of approximately 12 months of treatment, or the study ends, whichever occurs first. If needed, flush the IV line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Participants may be dosed Q4W ± 3 days for nivolumab.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 25 days from the previous dose of nivolumab during Q4W cycles. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab and/or ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.2.

Doses of nivolumab and ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment.

Please refer to the current IB and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

In Arm A and Arm B, participants may be retreated with nivolumab after completing 12 months of treatment during the Maintenance Period, if the participant has achieved disease control (CR, PR, or SD) and subsequently progresses. See Section 5.1.6.

7.1.2 Ipilimumab Dosing

In Arm A Maintenance Period, after the infusion of nivolumab, the infusion line should be flushed and the filters changed. Participants should then receive ipilimumab 1 mg/kg over an approximately 30 (± 5) minute infusion IV every 6 weeks (Q6W) starting on Day 1. Participants will be dosed Q3W ± 3 days for nivolumab and Q6W ± 3 days for ipilimumab. Treatment will continue until confirmed progression, unacceptable toxicity, withdrawal of consent, completion of approximately 12 months of treatment, discontinuation of nivolumab, or the study ends, whichever occurs first.

Ipilimumab dosing calculations should be based on the body weight. Dosing calculations should be based on the body weight assessed on C1D1 in Maintenance. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the baseline weight. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed. Participants may be dosed no less than 37 days from the previous dose of ipilimumab.

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.

Participants should be carefully monitored for infusion reactions during ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.2.

Doses of ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Use separate infusion bags and filters when administering nivolumab and ipilimumab on the same day.

For details regarding ipilimumab storage, preparation, and administration, please refer to the current IB and/or Pharmacy Manual.

In Arm A, participants may be retreated with nivolumab and ipilimumab after completing 12 months of treatment during the Maintenance Period, if the participant has achieved disease control (CR, PR, or SD) and subsequently progresses. Ipilimumab monotherapy is not permitted. See Section 5.1.6.

7.1.3 Durvalumab Dosing

In Arm C Maintenance Period, participants should receive durvalumab at a dose of 10 mg/kg as a 60 (± 5) minute infusion on Day 1 of each treatment cycle until confirmed progression, unacceptable toxicity, withdrawal of consent, completion of approximately 12 months of treatment, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of durvalumab allowed. Participants may be dosed Q2W ± 3 days. Premedications are not recommended for the first dose of durvalumab.

Participants should be carefully monitored for infusion reactions during durvalumab administration. If an acute infusion reaction is noted, participants should be managed according to the local durvalumab prescribing information.

Doses of durvalumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Please refer to the approved local Product Label for durvalumab for additional information.

7.1.4 Chemotherapy Dosing

During the CCRT Period, participants will be given chemotherapy for up to 3 cycles, with each cycle lasting 3 weeks. See Section 7.1.5 for option to skip cycle 1 of chemotherapy ± nivolumab alone if RT planning is completed prior to the first dose of therapy at Cycle 1. While etoposide/cisplatin and paclitaxel/carboplatin are applicable to any histology, participants with tumor of non-squamous histology have an additional option which is pemetrexed/cisplatin. In the case cisplatin cannot be given (eg, poor tolerability), carboplatin can replace cisplatin. The reasons must be recorded in the eCRF and medical record. In the case pemetrexed cannot be given (eg, poor tolerability), etoposide can replace pemetrexed. The reasons must be recorded in the eCRF and medical record.

7.1.4.1 Paclitaxel/Carboplatin Dosing

Each cycle of paclitaxel + carboplatin will last for 3 weeks. Treatment with paclitaxel and carboplatin will be administered as follows for Cycle 1, Cycle 2, and Cycle 3:

- Cycle 1; Day 1: carboplatin AUC 5 or 6 + paclitaxel 175 or 200 mg/m^2
- Cycle 2 and Cycle 3; Day 1, Day 8, and Day 15: carboplatin AUC 2 + paclitaxel 45 or 50 mg/m^2

Days 8 and 15 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment and per investigator's discretion. The carboplatin dose must be calculated according to Calvert formula. When calculating creatinine clearance (CrCl), the formula of Cockcroft-Gault (see below) should be used or per local standard:

- Calvert Formula: Dose (in mg) = Target AUC × (GFR + 25)
- Cockcroft-Gault: $\text{CrCl}\left(\frac{\text{mL}}{\text{min}}\right) = \frac{[140\text{-age (years)} \times \text{actual body weight (kg)}]}{72 \times \text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)} \times \{0.85 \text{ if female}\}$

Carboplatin doses (AUC 2 or AUC 5 or 6) will be administered IV over approximately 30 minutes (or per local standard).

Paclitaxel doses of 175 or 200 mg/m^2 will be administered IV over approximately 180 minutes (or per local standard). Paclitaxel doses of 45 or 50 mg/ m^2 will be administered IV over approximately 60 minutes (or per local standard).

7.1.4.2 Etoposide/cisplatin

Each cycle of etoposide + cisplatin will last for 3 weeks. Etoposide 100 mg/m^2 IV will be administered over approximately 60 minutes (or per local standard) on Day 1, Day 2, and Day 3 of each cycle. Days 2 and 3 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment and per investigator's discretion. Cisplatin will be administered at a dose of 80 mg/m^2 IV on Day 1 of each cycle. Recommended infusion time is approximately 60 minutes (or per local standard).

7.1.4.3 Pemetrexed/cisplatin

Each cycle of pemetrexed + cisplatin will last for 3 weeks. Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion (or per local standard) on Day 1 with cisplatin at a dose of 75 mg/m^2 as a 60-minute (or per local standard) IV infusion on Day 1 of each cycle. Pemetrexed should be infused before cisplatin on Day 1 of a cycle.

Pre-medications for use with pemetrexed are as follows:

- 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.
- Daily oral folic acid 350 mcg to 1000 mcg 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.
- Participants with non-squamous histology may begin folic acid and vitamin B12 prior to randomization in anticipation of administration of pemetrexed
- Antiemetic premedication may be given per local standard.

7.1.4.4 Carboplatin Dosing (with Etoposide or Pemetrexed)

In the event that carboplatin is administered instead of cisplatin with etoposide or pemetrexed, the reasons are to be documented in CRF as well as in medical record. Carboplatin at AUC 5 will be

given as a 30-minute (or per local standard) IV infusion on Day 1 of each 3 week cycle during CCRT. Carboplatin dose must be calculated according to Calvert formula. When calculating creatinine clearance (CrCl), the formula of Cockcroft-Gault should be used or per local standard.

7.1.4.5 Premedication

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. Doses of chemotherapy 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 (dose delays) and Section 8 (dose discontinuations).

Pre- and post-hydration for cisplatin should be administered per institutional protocol or per the following recommendation: Pre-treatment hydration of 1 to 2 liters of fluid infused IV prior to cisplatin infusion; Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Use of mannitol following the cisplatin infusion is allowed per local standard.

7.1.5 Radiotherapy Planning and Delivery

Each participant will receive thoracic radiotherapy in form of IMRT, VMAT, or 3DRT. Irradiation commences on D1 of Cycle 2 of systemic anticancer therapy (chemotherapy ± nivolumab) and will be delivered 5 days per week in once daily fraction, 2 Gy per fraction, to a target dose of 60-66 Gy in 30-33 fractions.

If radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 of the CCRT period (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. An additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy in this situation.

If the administration of systemic anticancer therapy at Cycle 2 must be delayed due to toxicity (for participants who start systemic treatment at Cycle 1), radiotherapy should start ± 3 days of start of systemic anticancer therapy in Cycle 2. It will not be considered a protocol deviation if chemoradiation is delayed for administrative reasons (eg, holidays), provided the full planned dose of radiotherapy is delivered. More detailed radiotherapy requirements can be found in the Thoracic Radiotherapy Guidelines, and QA & QC processes are subject to the CA20973L Radiotherapy Manual.

7.2 Method of Treatment Assignment

Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers

will not be reassigned. An IRT will be employed to manage participant randomization. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. Refer to the IRT manual for the information required for participant randomization. Please note that prior to randomization, the planned chemotherapy regimen, the planned number of cycles of chemotherapy (up to 2 cycles or up to 3 cycles), the planned dose level of chemotherapy at the start of treatment for agents with more than 1 possible dose level per protocol (eg, carboplatin, paclitaxel), and the radiation modality must be pre-defined and documented in the IRT and medical records by the investigator. Please note that if the actual treatment regimen administered to the participant during the CCRT Period changes from the planned regimen documented in the IRT prior to randomization, the rationale for the change must be recorded in the CRF and documented in the medical record.

Participants meeting all eligibility criteria will be randomized in a 1:1:1 ratio to 3 treatment arms and stratified by age, PD-L1 status, and stage (per AJCC staging system, 8th edition) as described below:

- Age:
  - <65 years old at time of randomization
  - ≥65 years old at time of randomization
- Tumor PD-L1 status (from IRT):
  - ≥1%
  - <1%
  - Indeterminate or not evaluable
- Stage (per AJCC 8th edition):
  - Stage IIIA
  - Stage IIIB
  - Stage IIIC

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of age, PD-L1 status, and AJCC Stage at Screening. The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

This is a randomized, open-label study. Blinding procedures are not applicable.

7.4 Dosage Modification

Dose reductions or dose escalations of nivolumab, ipilimumab, or durvalumab are not permitted in this study. Dose modifications for chemotherapy are allowed (see Section 7.4.5).

Dose Delay Criteria

- SARS-CoV-2 infection either confirmed or suspected.

Criteria to Resume Treatment

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**:

- at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen),
- resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications),
- evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and**
- consultation by the medical monitor.

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

7.4.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of nivolumab.

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

7.4.1.1 Criteria to Resume Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- For participants with Grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).
- Participants may resume treatment with study treatment if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Nivolumab therapy must be delayed until such time as this requirement is met. Please refer to Section 8.1.1 for special requirements for adrenal insufficiency.

Protracted delay or discontinuation of nivolumab during the CCRT Period does not prevent participants from entering the Maintenance Period in Arm A or Arm B if:

1) the delay or discontinuation is not due to nivolumab-related toxicities, and
2) eligibility criteria for initiation of the Maintenance Period are met.

In addition, nivolumab may not be resumed sooner than 18 days after the prior nivolumab dose.

7.4.2 Ipilimumab Dose Delay Criteria

Ipilimumab administration should be delayed as described in dose delay criteria for nivolumab in Section 7.4.

In addition, 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 retreatment criteria are met.

7.4.2.1 Criteria to Resume Ipilimumab

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 8.1.2) 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. Ipilimumab therapy must be delayed until such time as this requirement is met.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.2.
- Ipilimumab may not be resumed sooner than 37 days 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 18 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 Dose Delay Criteria for Durvalumab

Durvalumab-related toxicities should be managed according to the approved Product Label requirements for durvalumab. Please refer to the approved durvalumab Product Label for criteria to delay, resume, and discontinue durvalumab treatment.

7.4.4 Rescheduling Nivolumab and Ipilimumab for Arm A Maintenance Period:

- Ipilimumab should be infused on the same day as nivolumab on Day 1 of every cycle unless ipilimumab is delayed.
- On Day 22 visit of any cycle, if nivolumab dosing is delayed by more than 7 days, the dosing on the Day 22 visit within the cycle should be skipped. Dosing with both nivolumab and

ipilimumab may resume on D1 of the subsequent cycle as long as the minimum ipilimumab dosing interval is 37 days.

- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled with nivolumab as long as the minimum dosing interval for 2 consecutive nivolumab dosing is 18 days.
- 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.

7.4.4.1 Management Algorithms for Ipilimumab, Nivolumab, or Durvalumab

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Ipilimumab, nivolumab, and durvalumab 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 (see Appendix 6) and nivolumab and ipilimumab Investigator Brochures have been developed to assist investigators in assessing and managing the following groups of AEs:

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

Management algorithms for durvalumab may follow the principles aforementioned or per local approved Product Label requirements.

7.4.4.2 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 treatment 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).

7.4.5 Chemotherapy Dose Delay, Dose Modification, and Criteria to Resume Treatment

Clinical judgment should guide chemotherapy dose modifications in the study and follow local institutional standards and approved product labeling. When administering granulocyte colony stimulating factors (G-CSF) for supportive measures, local standard of care and approved product labeling should be utilized. After the first cycle of chemotherapy, G-CSFs may be used only to assist with hematologic recovery. General guidelines for coordinating chemotherapy, immunotherapy, and radiotherapy are listed below.

7.4.5.1 Etoposide or Pemetrexed + Platinum Regimens

1) During the CCRT Period, systemic anticancer therapy begins on Day 1 of Cycle 1 and radiotherapy begins on Day 1 of Cycle 2. However, if radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. An additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy in this situation.
2) When radiotherapy is initiated, systemic anticancer therapy and radiotherapy should be administered on the same day (i.e. Day 1), with radiotherapy administered after the completion of systemic anticancer therapy, if logistically feasible. Otherwise, a ± 3 day window will be permitted for the initiation of radiotherapy. For participants randomized to Arms A or B, chemotherapy must be administered after the completion of nivolumab administration AND on the same day nivolumab is administered.
3) Repeated chemotherapy dose delays are allowed if needed. If a single chemotherapy agent is delayed, the other chemotherapy agent(s) and nivolumab should be delayed. Nivolumab may resume only when criteria to resume both chemotherapy and nivolumab are met.
4) In the case that systemic anticancer therapy was administered during Cycle 1:
   a) If Cycle 2 chemotherapy is delayed, radiotherapy should not be initiated, and nivolumab not administered (in Arms A and B), until chemotherapy is resumed. Participants should be monitored at least on a weekly basis. If Cycle 2 chemotherapy is delayed for >3 weeks, then Cycle 2 chemotherapy should be skipped, and radiotherapy should be administered. The date of the first radiotherapy dose is defined as C2D1.
   b) If Cycle 2 chemotherapy is skipped, participants may receive nivolumab treatment on C2D1 for Arms A and B (± 3 days of initiation of radiotherapy).
   c) If Cycle 2 chemotherapy is discontinued, in Arms A and B, participants may receive nivolumab treatment on C2D1 (± 3 days of initiation of radiotherapy), and C3D1 (± 3 days of continuation of radiotherapy).

5) Regardless of whether Cycle 1 systemic anticancer therapy is skipped or not:
   a) If Cycle 3 chemotherapy is delayed, in Arms A and B, nivolumab should be delayed, but radiotherapy should continue as scheduled.
   b) If participant meets criteria to resume chemotherapy, chemotherapy (and nivolumab in Arms A and B) may be administered at any time during radiotherapy in Cycle 3.
   c) If Cycle 3 chemotherapy is discontinued, participants in Arms A and B may receive nivolumab treatment at any time during radiotherapy in Cycle 3.
   d) After the end of radiotherapy, any planned remaining systemic anticancer therapy that has yet to be dosed should be omitted.

7.4.5.2 Paclitaxel + Carboplatin Regimen

1) During the CCRT Period, systemic anticancer therapy begins on Day 1 of Cycle 1 and radiotherapy begins on Day 1 of Cycle 2. However, if radiotherapy planning is complete prior to the initiation of systemic anticancer therapy at Cycle 1 (Arms A, B, or C), the investigator has the option to skip Cycle 1 of systemic anticancer therapy alone, and initiate treatment with radiotherapy concurrently with systemic anticancer therapy (Cycle 2). All study procedures for Cycle 2 and Cycle 3 during the CCRT period are still to be followed. An additional cycle of consolidation systemic anticancer therapy will **not** be administered after the completion of radiotherapy in this situation.
2) When radiotherapy is initiated, systemic anticancer therapy and radiotherapy should be administered on the same day (i.e. Day 1), with radiotherapy administered after the completion of systemic anticancer therapy, if logistically feasible. Otherwise, a ± 3 days window will be permitted for the initiation of radiotherapy. For participants randomized to Arms A or B, chemotherapy must be administered after the completion of nivolumab administration AND on the same day nivolumab is administered.
3) Repeated chemotherapy dose delays are allowed if needed. If a single chemotherapy agent is delayed, the other chemotherapy agent(s) and nivolumab should be delayed. Nivolumab may resume only when criteria to resume both chemotherapy and nivolumab are met.
4) In the case that systemic anticancer therapy was administered during Cycle 1:
   a) If Cycle 2 chemotherapy is delayed, radiotherapy should not be initiated, and nivolumab not administered (in Arms A and B), until chemotherapy is resumed. Participants should be monitored at least on a weekly basis. Carboplatin + paclitaxel treatment in Cycle 2 and Cycle 3 entails 3 weekly doses in each cycle. Weekly doses that are delayed by more than 1 week should be skipped and the next weekly dose administered when criteria to resume chemotherapy are met. If Cycle 2 chemotherapy is delayed for >3 weeks, then Cycle 2 Day 1 chemotherapy should be skipped, and radiotherapy should be administered. The date of the first radiotherapy dose is defined as C2D1.

b) If Cycle 2 Day 1 chemotherapy is skipped, participants may receive nivolumab treatment on C2D1 (± 3 days of initiation of radiotherapy) in Arms A and B. If remaining weekly chemotherapy within C2 can resume afterwards, chemotherapy doses may be administered. From C2D8 onwards, if weekly chemotherapy is delayed beyond 7 days, this weekly chemotherapy should be skipped; if chemotherapy can't resume beyond two consecutive weeks, the chemotherapy should be discontinued.

c) If Cycle 2 chemotherapy is discontinued, participants may receive nivolumab treatment on C2D1 (± 3 days of initiation of radiotherapy), and C3D1 (± 3 days of continuation of radiotherapy).

5) If Cycle 1 systemic anticancer therapy was skipped:

a) From C2D8 and onwards, if weekly chemotherapy is delayed beyond 7 days, this weekly chemotherapy should be skipped; if chemotherapy can't resume beyond two consecutive weeks, the chemotherapy should be discontinued.

6) Regardless of whether Cycle 1 systemic anticancer therapy is skipped or not:

a) If Cycle 3 Day 1 chemotherapy is delayed, nivolumab (in Arms A and B) should be delayed, but radiotherapy should continue as scheduled.

b) If participant meets criteria to resume chemotherapy, chemotherapy (and nivolumab in Arms A and B) may be administered at any time during radiotherapy in Cycle 3 and the dose resumption date is defined as C3D1.

c) If the criteria to resume the remaining weekly chemotherapy within Cycle 3 are met, remaining C3D8 and/or C3D15 chemotherapy may be resumed as long as radiotherapy does not come to an end.

d) If Cycle 3 chemotherapy is discontinued, participants in Arms A and B may receive nivolumab treatment at any time during radiotherapy in Cycle 3.

e) After the end of radiotherapy, any planned remaining systemic anticancer therapy that has yet to be dosed should be omitted.

Chemotherapy toxicity may be managed per local standards. The following tables provide recommended delay and dose modifications for the following toxicities with cisplatin/carboplatin + etoposide or pemetrexed: Table 7.4.5.3-1 (Hematologic); Table 7.4.5.4-1 (Hepatic); Table 7.4.5.5-1 (Renal-Cisplatin); Table 7.4.5.5-2 (Renal-Carboplatin); and Table 7.4.5.6-1 (Other toxicities). Toxicity management recommendations for the carboplatin + paclitaxel regimen is provided in Section 7.4.5.7.

7.4.5.3 Cisplatin/Carboplatin + Etoposide or Pemetrexed Dose Modifications for Hematologic Toxicity

Dose modifications for hematologic toxicity are based on each pre-treatment blood count.

Table 7.4.5.3-1: Cisplatin/Carboplatin + Etoposide or Pemetrexed Dose Modifications for Hematological Toxicity

ANC x 10^9/l		Platelets x 10^9/l	Cisplatin + Etoposide or Cisplatin + Pemetrexed Carboplatin + Etoposide or Carboplatin + Pemetrexed
> 1.5 at day 1 of cycle	and	>100	Full dose
≤ 1.5 at day 1 of cycle	or	≤100	Delay until recovery ANC > 1.5 and platelets >100
Febrile neutropenia episode or treatment delay for grade 4 neutropenia > 7 days			Delay until recovery ANC > 1.5 and platelets >100 First event: full dose and G-CSF support is recommended. Second event (or if G-CSF support was already delivered): 20% dose reduction of both drugs and continuing G-CSF support.
		Grade 4 thrombocytopenia requiring medical intervention or grade ≥ 2 bleeding with thrombocytopenia	Delay until recovery ANC > 1.5 and platelets > 100 First event: 20% dose reduction of both drugs Second event: 35% dose reduction of both drugs

Abbreviations: ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.

7.4.5.4 Cisplatin/Carboplatin + Etoposide or Pemetrexed Dose Modifications for Hepatic Toxicity

It is possible that radiation may lead to abnormal liver function tests especially for lesions in the lower part of right lung. If these abnormalities are believed to be related to radiation only, no dose modification for chemotherapy is necessary.

Table 7.4.5.4-1: Cisplatin/Carboplatin + Etoposide or Pemetrexed Dose Modifications for Hepatic Toxicity

AST/ALT		Bilirubin	Cisplatin or Carboplatin	Etoposide or Pemetrexed
2-5 x ULN at day 1 of cycle	and	≤2 x ULN	Full dose	Full dose
> 5 x ULN at day 1 of cycle	or	> 2 x ULN	Delay one week then reassess using the same criteria. A delay up to three weeks is allowed (if a longer delay is necessary trial treatment must be stopped). First event: 20% dose reduction of etoposide at cycle 2 (or cycle 3 if first cycle systemic therapy is skipped), no reduction in carboplatin. Second event: 35% dose reduction of etoposide at cycle 3 (only applicable if systemic therapy is initiated at cycle 1).	

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

7.4.5.5 Cisplatin/Carboplatin + Etoposide or Pemetrexed Dose Modifications for Renal toxicity

Dose modifications for renal toxicity are shown in Table 7.4.5.5-1 for cisplatin and Table 7.4.5.5-2 for carboplatin. The calculated creatinine clearance should be determined before each course of chemotherapy.

Table 7.4.5.5-1: Cisplatin-based Chemotherapy Dose Modifications for Renal Toxicity (with Etoposide or Pemetrexed)

Calculated Creatinine Clearance at day 1 of Cycle	Cisplatin	Etoposide or Pemetrexed
> 50 ml/min	Full dose	Full dose
20-50 ml/min	Switch to carboplatin AUC 5	If pemetrexed is used, switch to etoposide with 25% dose reduction if < 45ml/min
< 20 ml/min	Off treatment	Off treatment

Abbreviation: AUC, area under the concentration-time curve.

Carboplatin-based chemotherapy dose modifications for renal toxicity are shown in Table 7.4.5.5-2.

Table 7.4.5.5-2: Carboplatin-based Chemotherapy Dose Modifications for Renal Toxicity (with Etoposide or Pemetrexed)

Calculated creatinine clearance at day 1 of cycle	Carboplatin	Etoposide or Pemetrexed
> 50 ml/min	Full dose	Full dose
20-50 ml/min	Full dose	If pemetrexed is used, switch to etoposide with 25% dose reduction if < 45ml/min
< 20 ml/min	Off treatment	Off treatment

7.4.5.6 Other toxicities with Cisplatin/Carboplatin + Etoposide or Pemetrexed

Other toxicities during treatment with cisplatin or carboplatin with etoposide or pemetrexed are listed in Table 7.4.5.6-1.

Table 7.4.5.6-1: Dose modifications for other toxicities with Cisplatin/Carboplatin + Etoposide or Pemetrexed

Severity	Modification
Peripheral neuropathy grade > 2	Switch to carboplatin AUC5 100% dose of etoposide
Grade 3-4 mucositis	50% dose of pemetrexed
Any grade 3-4 toxicities other than mucositis, nausea/vomiting, fatigue or alopecia	• 25% dose reduction for cisplatin/carboplatin and etoposide, or pemetrexed after recovery to grade ≤1. • A delay up to three weeks is allowed (if a longer delay is necessary treatment must be stopped).

Abbreviation: AUC, area under the concentration-time curve.

7.4.5.7 Dose Modifications for Toxicities with Carboplatin + Paclitaxel Regimen

Dose modification entails dose delay, skipping, and discontinuation. There are no dose reductions unless required by local standards. Hematological and non-hematological toxicities are listed in Table 7.4.5.7-1 and Table 7.4.5.7-2, respectively.

Table 7.4.5.7-1: Carboplatin + Paclitaxel Dose Modifications for Hematological Toxicities

Severity	Paclitaxel	Carboplatin
Thrombocytopenia grade > 1	Hold until grade ≤ 1	Hold until grade ≤ 1
Other hematological toxicities grade ≥ 3 except for leukopenia and lymphopenia	Hold until grade ≤ 2	Hold until grade ≤ 2

Table 7.4.5.7-2: Carboplatin + Paclitaxel Dose Modifications for Non-Hematological Toxicities

Severity	Paclitaxel	Carboplatin
Neuropathy grade 2 Neuropathy grade ≥ 3	Hold until grade ≤ 1 Discontinue	Maintain dose Discontinue
Febrile neutropenia	Hold	Hold
CrCl < 20 ml/min	Maintain dose	Discontinue
Allergic reaction grade ≥ 3	Discontinue	Discontinue
Other non-hematological toxicities grade ≥ 3	Hold until grade ≤ 2	Hold until grade ≤ 2

Abbreviation: CrCl, creatinine clearance.

If weekly low dose chemotherapy cannot resume beyond 7 days, this dose should be skipped. If weekly dose cannot resume beyond 2 consecutive weeks, chemotherapy should be permanently discontinued.

7.4.6 Radiotherapy Dose Modification

In principle, radiotherapy should continue with ≤ Grade 3 non-hematological toxicities and should be held for Grade 4 non-hematological toxicities, then resume when toxicities resolve to ≤ Grade 2. Holding radiotherapy for Grade 4 hematological toxicities other than lymphopenia and leukopenia may be considered.

7.4.6.1 Esophagitis from Radiotherapy

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Participants should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous xylocaine, carafate, or other medications should be used for symptomatic relief. As the esophageal transit time is clearly prolonged with radiotherapy and reflux may occur, the use of PPIs or H2 antagonists is recommended. Opioids may be required, especially in managing high grade esophagitis. In case of Grade 2 esophagitis occurring during the first 2 weeks of radiotherapy, a fungal infection, mainly candida albicans, may have occurred. Treatment with anti-fungal agents such as nystatin or fluconazole should be considered.

Acute esophagitis may persist for 4-6 weeks. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to ≤ 3 treatment days. Participants requiring hospitalization because of esophagitis may have their treatment interrupted.

Acute esophageal toxicity should be pharmacologically managed with the recommended treatment options per local standard practice and should be initiated at the first signs or symptoms of esophageal toxicity. See Table 7.4.6.4-1 for recommended management of high grade esophagitis.

7.4.6.2 Pulmonary Toxicity from Radiotherapy

See Table 7.4.6.4-1.

7.4.6.3 Skin Toxicity from Radiotherapy

See Table 7.4.6.4-1.

7.4.6.4 Combined Chemoradiotherapy Dose Modifications

Table 7.4.6.4-1: Chemoradiotherapy Modifications for In-Field Toxicities

Toxicity	CTCAE v 4.0 Grade	Radiotherapy	Chemotherapy
Esophagus/pharynx	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx	3	No change or hold ≤ 5 days	Hold treatment until ≤ Grade 2
Esophagus/pharynx	2	No change	No change

Table 7.4.6.4-1: Chemoradiotherapy Modifications for In-Field Toxicities

Pulmonary	4	Discontinue	Discontinue
Pulmonary	3	Consider to hold until ≤ Grade 2	Consider to hold until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	3	No change	No change

Abbreviation: CTCAE v 4.0, Common Terminology Criteria for Adverse Events version 4.0.

Additional chemoradiotherapy modifications are as follows:

1) If treatment is interrupted ≥ 3 weeks for pneumonitis, discontinue all protocol therapy in CCRT period.
2) In case of interruptions due to machine breakdown or public holidays or any interruptions of therapy up to 7 days, radiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported
3) In the case of Grade 3 esophagitis related to the concomitant treatment, chemotherapy should be suspended if the investigator believes continued use will jeopardize the delivery of full-dose radiotherapy; radiation is to be continued

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, 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 approved Product Label.

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 CA20973L Study Manual.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Study treatment will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited and/or restricted during the study (unless utilized to treat a drug-related adverse event or as premedication):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent anti-neoplastic therapy other than specified as study treatments (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose
- Investigators should refer to the approved local product labeling for the chemotherapy drugs for additional prohibited and restricted concomitant medications. After the first cycle of chemotherapy, prophylactic G-CSFs can be administered only to assist with hematologic recovery.

7.7.2 Prior and Concomitant Medications

Any medications (prescription and OTC), vitamin and mineral supplements, and/or herbs taken by the participant from screening through the treatment phase of the study will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for any procedure are encouraged to be included.

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study.

7.7.3 Other Restrictions and Precautions

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 of 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.

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of

randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

7.7.4 Imaging Restriction and Precaution

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

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

7.8 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 study drug 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

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Completion of the course of study treatment
- Termination of the study by Bristol-Myers Squibb (BMS)

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue on the study. Strict conditions apply and BMS approval is required.)
- Disease progression in the absence of clinical benefit as determined by the Investigator
- See Section 8.1.1, Section 8.1.2, Section 8.1.3, Section 8.1.4, and Section 8.1.5 for discontinuation criteria for nivolumab, ipilimumab, durvalumab, chemotherapy, and CCRT, respectively.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor

If a participant has not progressed following discontinuation of study treatment(s), every effort should be made to continue to obtain radiographic tumor assessments until BICR confirmed progression and Investigator-assessed distant metastases.

A participant may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs).

Participants may choose to discontinue the study at any time, for any reason, and without prejudice to further treatment.

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

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

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Table 2-8. 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 per local regulatory requirements in each region/country and entered on the appropriate case report form (eCRF) page.

8.1.1 Discontinuation Criteria for Nivolumab

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

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS medical monitor or designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation (exception is for nivolumab 480 mg Q4W where the delay can last up to 10 weeks), with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose (> 10 weeks for nivolumab 480 mg Q4W) that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (> 10 weeks for nivolumab 480 mg Q4W), the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Nivolumab should be discontinued for 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.

NOTE: For participants in Arm A, during the Maintenance Period, receiving nivolumab in combination with ipilimumab, 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 the investigator is unable to determine whether the event is related to nivolumab, or ipilimumab, the participant should discontinue all treatment: and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

8.1.2 Ipilimumab Discontinuation Criteria

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 treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(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.
- 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 the investigator is unable to determine whether the event is related to nivolumab or ipilimumab, the participant should discontinue nivolumab and ipilimumab.

8.1.3 Durvalumab Discontinuation Criteria

The toxicity management strategy for durvalumab (see Section 7.4.3) may lead to discontinuation or resumption of durvalumab upon clinical outcomes. See local approved prescribing information for durvalumab.

8.1.4 Discontinuation Criteria for Chemoradiotherapy

As highlighted in dose modification for chemotherapy (see Section 7.4.5) and chemoradiation (see Section 7.4.6), despite diligent management, if toxicities remain unmanageable, components in question should be discontinued.

Specifically, one or both chemotherapy components should be discontinued for any of the following:

- Grade ≥3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related grade 3/4 adverse event (eg, ANC, PLT) 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 drug-related liver function test (LFT) abnormality that meets the following criteria:
  - 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 Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) that is suspected to be causing the reaction. The drug(s) not suspected to be related to the hypersensitivity reaction or infusion reaction may be continued
- In case of renal toxicity, if CrCl ≤ 50 mL/min but ≥ 20 mL/min, cisplatin should be discontinued and a switch to carboplatin at AUC 5 could be opted for. 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-based doublet cycles when the participant meets retreatment criteria. Carboplatin should be discontinued if CrCl < 20 mL/min. In case of CrCl < 45 mL/min, pemetrexed should be discontinued and may be substituted with etoposide with 25% dose reduction. In case of CrCl < 20 mL/min, any chemotherapy should be stopped
- Participants with non-hematologic toxicities ≥ Grade 3 (excluding neurotoxicity), pemetrexed should be withheld until resolution to better than or equal to baseline
- In case of peripheral neuropathy grade > 2, cisplatin should be stopped and be substituted by carboplatin at AUC 5. Stop chemotherapy for Grade 3/4 neurotoxicity, except for carboplatin which may be withheld until ≤ Grade 2
- Any Grade 4 drug-related adverse event which the investigator deems 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.
- Regarding rules of dose skipping or discontinuation due to exceeding the maximum dose delay, please refer to Section 7.4.5.
- 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 chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any participant for additional guidance on dose discontinuation.

8.1.5 Multimodality in CCRT Period Discontinuation Criteria

In cases where one or a few components in the multimodality therapy meet discontinuation criteria, other components may continue as judged appropriate by investigator. It is of ultimate importance to try the best to deliver radiotherapy as planned without delay or interruption. Full supportive care should be in place. Chemotherapy (and/or nivolumab) may be delayed or discontinued to ensure the delivery of radiotherapy. Maintaining the planned cumulative platinum chemotherapy dose takes the second priority, followed by nivolumab in Arm A and Arm B.

8.1.6 Treatment beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[20]

Participants will be permitted to continue maintenance treatment in Arm A, Arm B, and Arm C beyond initial RECIST 1.1 defined PD, as assessed by the investigator, for up to a maximum of 12 months from date of first dose, as long as they meet the following criteria:

1) Investigator-assessed clinical benefit.
2) Tolerance of study treatment
3) Stable performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5) Participant provides written informed consent prior to receiving additional maintenance treatment.
6) Crossover between study treatments/arms is not allowed.

All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

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

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the treatment and continue to receive monitoring according to Section 2 (Schedule of Activities).

For the participants who continue study treatment beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Treatment should be discontinued permanently upon documentation of further progression.

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

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a

participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the 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 eCRF 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 this study, PFS and OS are key endpoints. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed 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.

[redacted]

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

8.2.1 Post Study Treatment Follow-up

In this study, PFS-2 is an important endpoint. Post study follow-up, including subsequent treatment/progression, is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Participants who discontinue study treatment may continue to be followed.

8.3 Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 Section 2: 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 Section 2: Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure (and in Appendix 6).

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

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images must be submitted to a central imaging vendor for blinded independent central review (BICR). Prior to scanning the first participant sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA20973L Imaging Manual provided by the central imaging vendor. Screening and on study images should be acquired as outlined in Section 2 (Schedule of Activities).

Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) for RECIST 1.1 tumor assessment and submit to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, x-rays and bone scans do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of the abdomen, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

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

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

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

Use of CT component of a PET-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in

anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

MRI of brain must be acquired as outlined in Section 2 (Schedule of Activities). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated or based on Investigator discretion.

9.1.1.2 Clinical Assessment and Imaging

Tumor assessments should continue at the same frequency even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using RECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST 1.1 criteria (see Appendix 8 for specifics of RECIST 1.1 criteria to be utilized in this study). Specific to this study, lesions that received irradiation during the CCRT Period and remain measurable, continue to be considered measurable. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A best overall response of SD requires a minimum of 56 days on study from randomization to the date of the first imaging assessment.

Tumor assessment by the Investigator must continue until distant metastases is assessed by the Investigator per RECIST 1.1.

9.1.1.3 BICR Confirmation of Progression or Recurrence

Sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study until PD is confirmed by the BICR. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR review will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated for submission to BICR. Also, if participants discontinue treatment without BICR confirmed radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2 (Schedule of Activities) for submission to the BICR until progression has been confirmed by BICR. If the planned start of subsequent anticancer therapy is sooner than the time of next scheduled tumor assessment, every effort should be made to repeat tumor imaging prior to initiation of subsequent anticancer therapy unless clinically infeasible.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment. Tumor assessment by the Investigator must continue until Investigator-assessed distant metastases, as noted above.

9.1.2 Outcomes Research Assessments

The evaluation of patient-reported outcomes is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life measures provide data needed for calculating utility values to inform health economic models.

Participants will be asked to complete the Functional Assessment of Cancer Therapy – Lung Cancer (FACT-L) Module, the Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire (NSCLC-SAQ), 5-level version of the EuroQol Group's EQ-5D (EQ-5D-5L) and the Patient Global Impression of Severity (PGI-S).

The NSCLC-SAQ, PGI-S, FACT-L, and EQ-5D-5L will be administered via an electronic device during specified clinic visits, and will be completed prior to any other assessments or study procedures when they are being administered during study visits. In addition, the PRO measures will be completed at designated time points during the long-term Follow-up Period and entered into the CRF. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative.

Section 2 (Schedule of Activities) provides information regarding the timing of PRO assessments during the CCRT Period, Recovery Period, Maintenance Period, and during the long-term Follow-up Period.

Additional information about the timing of each assessment is described below.

9.1.2.1 FACT-L

The Functional Assessment of Cancer Therapy – Lung (FACT-L) cancer module, is a widely-used, reliable, and valid measure of multidimensional health status among people who have lung cancer. The FACT-L scale is a 36-item self-report instrument that measures multidimensional QOL by asking participants to rate a series of statements on a 5-point Likert scale. The FACT-L, version 4, is a combination of the 27-item FACT-General (FACT-G) and the 9-item Lung Cancer Subscale

(LCS). A subset of the 7 items from FACT-L (2 of the 9 items are not scored, and will not be administered) will be used to calculate the LCS, which will be used to assess disease-specific symptom severity.

A total FACT-G score is calculated by summing the physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) subscale scores. A total FACT-L score is obtained by summing the FACT-G score with the LCS, thereby augmenting the FACT-G with lung cancer–specific QOL information. The FACT-L also contains the GP5 item from the FACT-G, which is used to assess the bother associated with the side effects of treatment. Each of the items is scored on a five-point scale from zero (Not at all) to four (Very much). Higher scores indicate greater quality of life. The FACT-L uses a recall period of "the past 7 days."

The FACT-L will be administered per Section 2 (Schedule of Activities).

9.1.2.2 Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)

The NSCLC-SAQ is a 7-item PRO measure intended for use in advanced NSCLC clinical trials to support medical product labelling.[45] The NSCLC-SAQ uses a 7-day recall period and verbal rating scales. It was developed in accordance with the US Food and Drug Administration's PRO Guidance and scientific best practices, and the resulting qualitative interview data provide evidence of content validity. The NSCLC-SAQ total score measures overall severity of the following NSCLC symptoms: cough, pain, dyspnea, fatigue, and appetite. The NSCLC-SAQ has been qualified for exploratory use to measure symptoms of non-small cell lung cancer in drug development programs. Further evaluation is needed on the instrument's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change in score. After the NSCLC-SAQ's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change have been evaluated, the NSCLC-SAQ total score is intended to support labeling claims related to change in overall symptoms of NSCLC. Data from this study will help to interpret the psychometric properties and threshold for clinically meaningful within-patient change in the NSCLC-SAQ total score within locally advanced untreated NSCLC participants.

The NSCLC-SAQ will be administered per Section 2 (Schedule of Activities).

9.1.2.3 EQ-5D-5L

The EQ-5D-5L[46] is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels, reflecting no problems, slight problems, moderate problems, severe problems and extreme problems. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively, as described by the EQ-5D-5L. Altogether, the instrument describes $5^5 = 3{,}125$ health states.

Empirically-derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate an index measuring the value to society of his or her current health. [47] Utility index values range from a 1 (full health) to 0 (dead) with negative values indicating a state considered worse than being dead. In addition, the EQ-5D-5L includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 0-100 point scale ranging from "the worst health you can imagine" to the "best health you can imagine." The EQ-5D-5L uses a recall period of "today."

The EQ-5D-5L will be administered per Section 2 (Schedule of Activities).

9.1.2.4 Patient Global Impression of Severity (PGI-S)

PGI-S will be included as an additional exploratory endpoint. The PGI-S is a single item that assesses participant's perceptions of overall severity of cancer symptoms for the last 7 days with response options ranging from "none" to "very severe." Data collected via the PGI-S will be used as an anchor measure to assess the psychometric measurement properties and the threshold for meaningful change for the NSCLC-SAQ.

The PGI-S will be administered per Section 2 (Schedule of Activities).

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 acceptable representative).

The investigator and any qualified 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 are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Collect all nonserious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. See Section 9.2.3 for additional details on Follow-up.

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

All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of signing the consent and within 100 days following discontinuation of dosing.

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

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

For participants randomized to treatment and never treated with study treatment, collect SAEs for 30 days from the date of randomization.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 9.2, and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases of SARS-CoV-2, until infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the 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 Regulation EU No. 536/2014 and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 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. Pregnancy reporting must follow the same transmission timing and processes to BMS as those used for SAEs, in accordance with reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/sponsor/IRB/EC, as applicable.

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

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

In cases where a study treatment can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred

between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

1) Aminotransaminases (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.

9.2.8 Other Safety Considerations

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

9.2.8.1 Immune-mediated Adverse Events

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

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. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

9.4 Safety

Planned time points for all safety assessments are listed in Section 2: Schedule of Activities.

9.4.1 Physical Examinations

See Schedule of Activities.

9.4.2 Vital Signs

Vital sign measurements will be recorded per Section 2 (Schedule of Activities). Vital signs include heart rate, systolic and diastolic blood pressure, and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible.

9.4.3 Electrocardiograms

All participants will have 12-lead electrocardiogram (ECG) done during Screening and at End of the Recovery Period, as specified in the Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

A list of the clinical laboratory analyses to be tested is provided in Table 9.4.4-1. All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2).

Investigators must document their review of each laboratory safety report. The Investigator or qualified Sub-Investigator will review all results for clinical significance. Any laboratory result deemed clinically significant (ie, is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 9.2.

Table 9.4.4-1: Clinical Safety Laboratory Assessments

Hematology -CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum urea Glucose	Albumin Sodium Potassium Chloride Calcium Phosphorus CK TSH, free T3, and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on D1 of each treatment cycle (except for Arm C in the CCRT period only)
Serology	
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA), - screening only. Testing does not need to be repeated during re-enrollment if the previous testing is performed within 45 days prior to randomization. Testing for HIV at screening must be performed where mandated by local requirements.	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55	
Urinalysis - screening only and as clinically indicated.	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; FSH, follicle stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; HBV, hepatitis B virus; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; RNA, ribonucleic acid; sAG, surface antigen; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics

Pharmacokinetic (PK) and immunogenicity (IMG) assessment data will be collected from study participants in the treatment arms receiving nivolumab and ipilimumab (Arm A and Arm B) at the time points indicated in Table 9.5-1, Table 9.5-2, Table 9.5-3, and Table 9.5-4. All time points are

relative to the start of the first study drug administration. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. Serum PK samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Additionally, selected serum PK samples may be analyzed by exploratory and/or research methods that measure nivolumab and/or ipilimumab; exploratory/research results will not be reported.

Immunogenicity samples will be analyzed for anti-nivolumab/ipilimumab antibodies by validated immunogenicity assays. Samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by exploratory and/or research methods that measures anti-drug antibodies for technology exploration purposes; exploratory/research results will not be reported. Serum/plasma samples designated for PK or [redacted] may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling in Arm A (CCRT)

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time (Relative to Nivolumab Infusion) Hour:Min	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X
	EOI[b]	00:30	X	
Cycle 2 Day 1	Predose[a]	00:00	X	X
	EOI[b]	00:30	X	
Cycle 3 Day 1	Predose[a]	00:00	X	

Abbreviations: CCRT, concurrent chemoradiotherapy; Cmax, maximum concentration; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic.

[a] Take all predose samples for nivolumab prior to the start of nivolumab infusion.

[b] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling in Arm A (Maintenance)

Study Day of Sample Collection[a] (1 Cycle = 6 Weeks)	Event	Time (Relative to Nivolumab Infusion) Hour:Min	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample	Ipilimumab PK Serum Sample	Ipilimumab IMG Serum Sample
Cycle 1 Day 1	Predose[b]	00:00	X	X	X	X
	EOI[c]	See footnote c	X		X	
Cycle 1 Day 22	Predose[b]	00:00	X	X	X	X
Cycle 2 Day 22	Predose[b]	00:00	X	X	X	X
Cycle 5 Day 22	Predose[b]	00:00	X	X	X	X
Cycle 7 Day 22	Predose[b]	00:00	X	X	X	X

Abbreviations: Cmax, maximum concentration; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic.

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and IMG should be collected only for the next 1 time point (corresponding to nivolumab sample collection) according to the PK table.

[b] Take all predose samples for nivolumab and ipilimumab prior to the start of nivolumab infusion.

[c] The EOI sample for both nivolumab and ipilimumab should be collected at the end of ipilimumab infusion. Since the EOI-PK sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling in Arm B (CCRT)

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Event	Time (Relative to Nivolumab Infusion) Hour:Min	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X
	EOI[b]	00:30	X	
Cycle 2 Day 1	Predose[a]	00:00	X	X
	EOI[b]	00:30	X	
Cycle 3 Day 1	Predose[a]	00:00	X	

Abbreviations: CCRT, concurrent chemoradiotherapy; Cmax, maximum concentration; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic.

[a] Take all predose samples for nivolumab prior to the start of nivolumab infusion.

[b] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling in Arm B (Maintenance)

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event	Time (Relative to Nivolumab Infusion) Hour:Min	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X
	EOI[b]	00:30	X	
Cycle 2 Day 1	Predose[a]	00:00	X	X
Cycle 4 Day 1	Predose[a]	00:00	X	X
Cycle 8 Day 1	Predose[a]	00:00	X	X
Cycle 12 Day 1	Predose[a]	00:00	X	X

Abbreviations: Cmax, maximum concentration; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic.

[a] Take all predose samples for nivolumab prior to the start of nivolumab infusion.

[b] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

9.6 Pharmacodynamics

See Section 9.8.

9.7 Pharmacogenomics

See Section 9.8.

9.8 Biomarkers

[redacted] Tumor tissue will be collected at [redacted]

Table 9.8-1: Biomarker Collection Schedule for CCRT Period for All Arms

Study Day of Sample Collection (1 Cycle = 3 Weeks)	Tumor (Archival or Fresh biopsy in FFPE)
Screening	X
Cycle 1 Day 1	
Cycle 2 Day 1	
Cycle 3 Day 1	
Upon Progression	

Abbreviations: CCRT, concurrent chemoradiotherapy;

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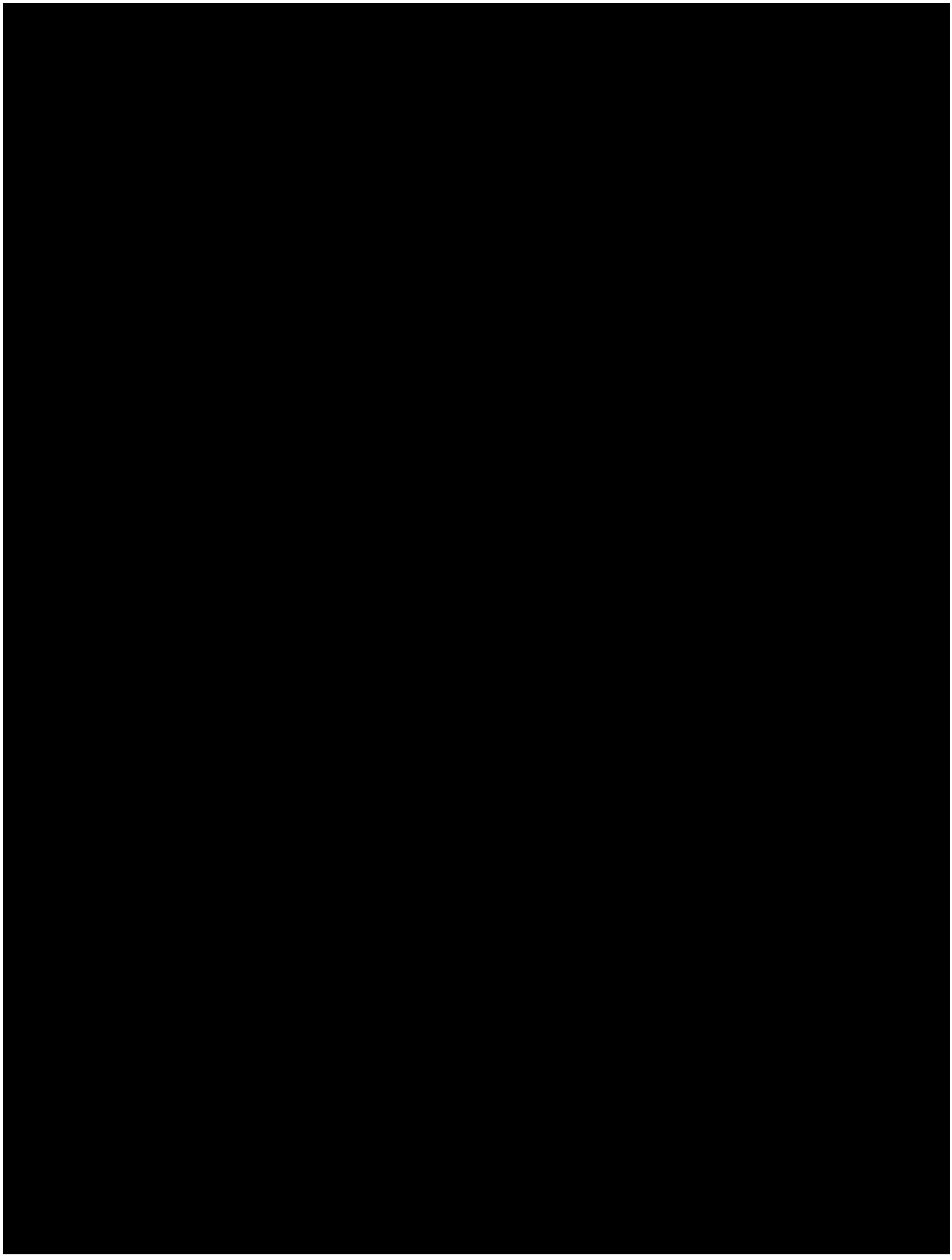
9.8.1 Tumor Tissue Specimens

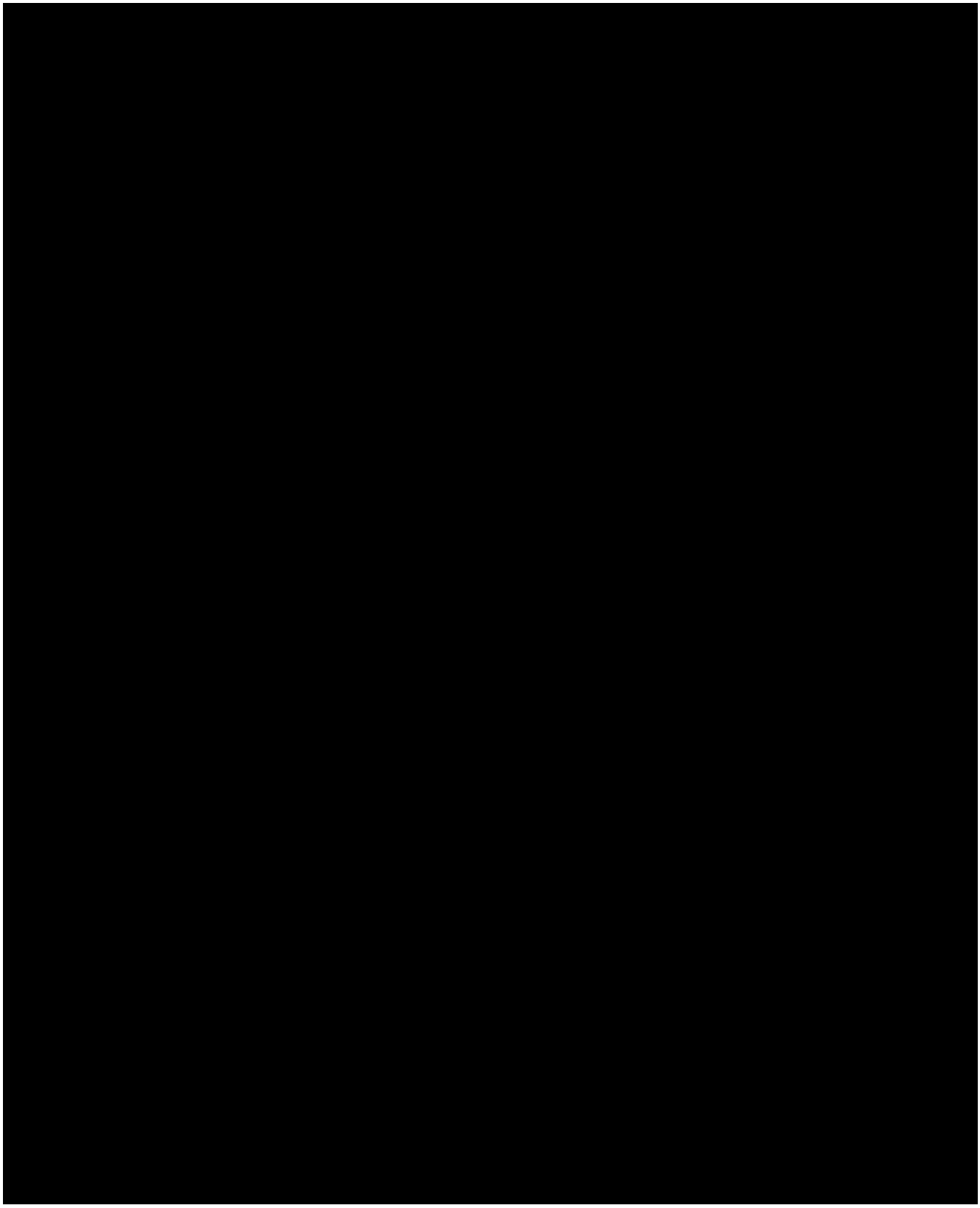
Archival (or fresh) FFPE tumor tissue is to be collected within 3 months prior to enrollment with no intervening systemic anti-cancer treatment between time of acquisition and randomization. A sample block or 5 to 10 unstained slides must be submitted to the central laboratory. In order for the participant to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the Screening Period.

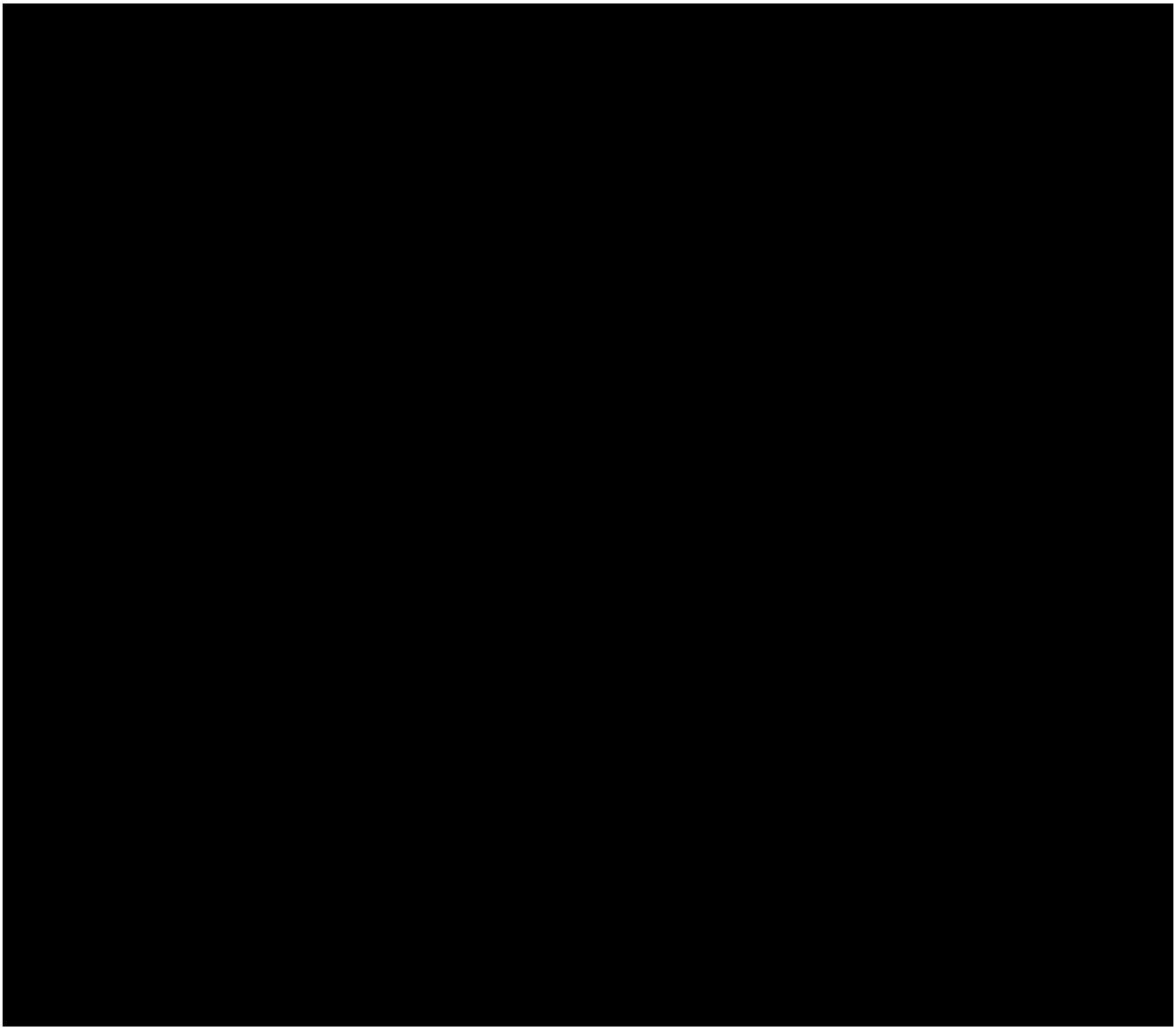
[redacted]

Tumor samples must be a core biopsy, excisional biopsy, or surgical specimen. Biopsy of pathological lymph nodes can be submitted. Fine needle aspirates/biopsy or other cytology specimens are insufficient for enrollment. Target lesion should not be biopsies unless there are no other lesions suitable for biopsy. If a target lesion is used for biopsy, the lesion must be > 2 cm in the longest diameter.

[redacted]







9.9 Medical Resource Utilization and Health Economics

Health care resource utilization data will be collected for all randomized participants using an internal eCRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

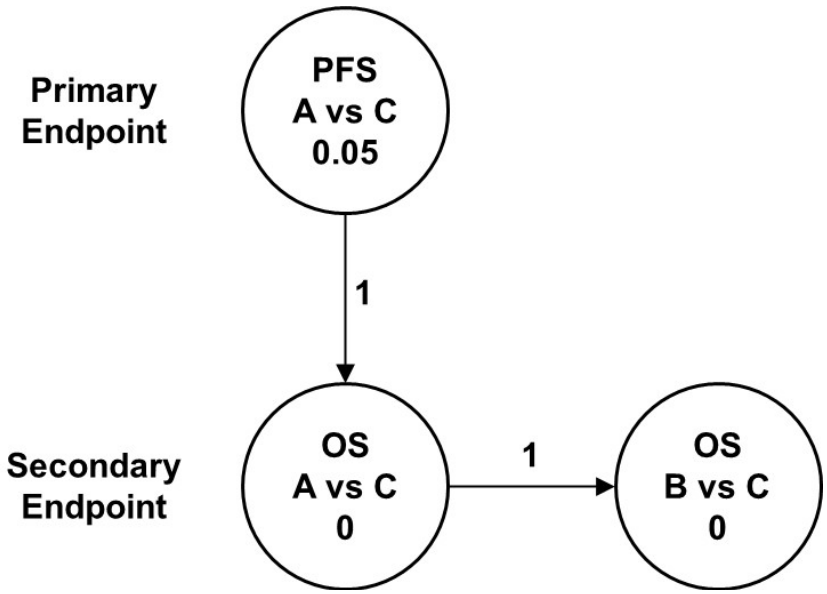
10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size is determined based on the primary endpoint of PFS between Arm A and Arm C. A total of 888 participants are planned to be randomized across the 3 treatment groups in a 1:1:1 ratio.

If the PFS comparison between Arm A and Arm C is statistically significant, then 0.05 alpha will be passed to the OS comparison between Arm A vs Arm C, followed by OS comparison between Arm B vs Arm C. All tests will be 2-sided. Figure 10.1-1 graphically presents the planned testing procedure.

Figure 10.1-1: Testing Procedure for Primary and Key Secondary Endpoints



Abbreviations: OS, overall survival; PFS, progression-free survival.
Note: Arms A, B, and C are described in Section 5.1.

UPDATE: Due to the Ukraine-Russia conflict, the Sponsor made the decision to discontinue clinical trials in Russia by the end of June 2022 as a result of increased logistical challenges of ensuring continuity of care for study participants. The study team performed an assessment of data quality and concluded that data collected among Russian participants (30 randomized) appeared adequate for inclusion in the primary analysis, though many participants would not be able to receive the full course of their randomized intervention and would have short follow-up. A sensitivity analysis for exclusion of all Russian participants is planned. Consequentially, enrollment was permitted to continue slightly beyond the original target of 888 randomized participants to account for potential data and statistical power loss in Russian sites and, ultimately, 925 participants were randomized.

10.1.1 Sample Size Justification for PFS

Based on the 4-year update from the PACIFIC trial and the PROCLAIM PFS curve,[3,10] a non-constant PFS hazard was observed. For the sample size calculation for PFS per BICR between Arm A and Arm C, a piecewise exponential distribution with a 3-month delay period was assumed. [redacted]

A total of [redacted] (ie, progression events or deaths) in Arms A and C will provide approximately 82% power considering the above PFS assumptions with 0.05 2-sided alpha. Two formal PFS interim analyses are planned at [redacted] of total planned PFS events as described in Table 10.1.1-1. [redacted] The stopping boundaries for the above PFS interim and final analyses will be based on the actual number of PFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

[redacted] However, the PFS analyses are driven by the required number of events, and the actual analysis time will depend on actual enrollment speed and events accrual and may be different from projections.

[redacted]

Table 10.1.1-1: Summary of Sample Size Parameters

Primary Endpoint	**PFS**
Comparison	Arm A vs Arm C
Sample size (Arm A and Arm C)	592
Overall Alpha	0.05
Overall Power	~82%

Table 10.1.1-2: Summary of Sample Size Parameters

Primary Endpoint	**PFS**
Comparison	Arm A vs Arm C
Sample size (Arm A and Arm C)	592
Overall Alpha	0.05
Overall Power	~82%

Table 10.1.1-2: Summary of Sample Size Parameters [redacted]

Primary Endpoint	PFS
[redacted]	

10.1.2 Sample Size Justification for OS

[redacted] will provide approximately 80% power, respectively, to detect above OS assumption.

[redacted]. OS will only be formally tested if PFS is significant. If PFS is significant but a significant OS benefit is not observed, then subsequent OS analyses will be triggered by accumulating OS events as described in Table 10.1.2-1. 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 a separate Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

[redacted] However, the timing of the OS final analysis is based on OS events accrual rate from an exponential distribution. Assuming a lower events rate towards the end of the curve, the final analysis may occur later.

[redacted]

Table 10.1.2-1: Summary of Sample Size Parameters and Projected Schedule of Analyses for OS [redacted]

Key Secondary Endpoint	**OS[a]**
Comparison	Arm A vs Arm C
Sample size (Arm A and Arm C)	592
[redacted]	
Overall Power	~80%
[redacted]	

Abbreviations: OS, overall survival; PFS, progression-free survival.

[a] OS will be tested only if PFS is significant.

Table 10.1.2-2: Summary of Sample Size Parameters and Projected Schedule of Analyses for OS [redacted]

Key Secondary Endpoint	**OS[a]**
Comparison	Arm A vs Arm C
Sample size (Arm A and Arm C)	592
[redacted]	
Overall Power	~80%
[redacted]	

Abbreviations: [redacted]; OS, overall survival; PFS, progression-free survival.

[a] OS will be tested only if PFS is significant.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who sign an informed consent form and are registered into the IRT
ITT Population / All Randomized Participants	All enrolled participants who are randomized to any treatment arm in the study. This is the primary population for efficacy and baseline characteristics
Safety Population / All Treated Participants	All enrolled participants who received at least one dose of study treatment. This is the primary population for overall dosing and safety
Maintenance Therapy Treated Participants	All participants who completed CCRT period and received at least one dose in the maintenance period. This is primary population for maintenance dosing and safety
PK and immunogenicity participants	All treated participants with available serum time-concentration data and immunogenicity samples from randomized participants dosed with nivolumab and/or ipilimumab.
[redacted]	

Abbreviations: CCRT, concurrent chemoradiotherapy; IRT, Interactive Response Technology; ITT, intent-to-treat; PK, pharmacokinetic.

10.3 Statistical Analyses

In general, continuous data will be summarized by descriptive statistics, including number of participants, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of participants. Unless otherwise specified, data will be summarized by treatment arm.

No formal testing for PFS between Arm B vs Arm C nor PFS/OS for Arm A vs Arm B will be performed. These evaluations will be performed descriptively, as outlined in the statistical analysis plan.

A detailed description of analysis methods will be provided in the statistical analysis plan (SAP).

The statistical analysis plan will be developed and finalized before the first efficacy interim database lock. The SAP 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 analyses	
Progression-free Survival (per BICR) A vs C	Progression-free survival (PFS) is defined as the time between the date of randomization and the first date of documented progression per RECIST 1.1, as determined by BICR, or death due to any cause, whichever occurs first, regardless of receipt of subsequent anti-cancer therapy prior to the documented progression as confirmed by BICR. Participants who die without a reported 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 and did not die will be censored on their date of randomization. First on-study scans are expected only after completion of CCRT (ie, last dose of radiotherapy) during approximately the Week 3 Recovery Period check. Following that, tumor assessments are scheduled to be performed at week 24 (±7 days) from the date of randomization, then every 12 weeks (±7 days) for 36 months (from date of randomization), then every 24 weeks (±7 days) after 36 months from randomization. Tumor assessments will be submitted to BICR until BICR-confirmed disease progression. A log-rank test stratified by 3 stratification factors (age, PD-L1 status, and stage) will be used to compare PFS between Arm A and Arm C at 0.05 level. A Cox proportional hazards model with treatment as the single covariate, stratified by the above stratification factors, will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize PFS, including PFS curves, medians with corresponding 95% CIs. The PFS rates at 6, 12, 18, 24, etc months will also be estimated depending on minimum follow-up duration.
Secondary/Exploratory analyses	
Overall Survival A vs C B vs C A vs B	Overall survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a participant was known to be alive. OS will be followed continuously while participants are on the study treatment and every 3 months via in-person or phone contact after participants discontinue the study treatment. OS will be analyzed using similar method as PFS. OS in A vs C, B vs C will be tested following the hypothesis testing procedure described in Section 10.1. No hypothesis testing will be performed for A vs B.
Progression-free Survival (per BICR) B vs C A vs B	See definition and methods of PFS in primary statistical analysis methods above. No hypothesis testing will be performed.

Endpoint	Statistical Analysis Methods
Objective Response Rate (ORR) per BICR A vs C B vs C A vs B	Objective Response Rate (ORR) is defined as the number of participants with a confirmed BOR of CR or PR divided by the number of randomized participants for each treatment group. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 as determined by BICR or the date of initiation of local therapy or the date of subsequent anticancer therapy, whichever occurs first. For participants without documented progression or local therapy or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For participants who continue study medication beyond progression, the BOR should be determined based on response designations recorded at the time of the initial RECIST 1.1 defined progression. An odds ratio and 95% confidence interval (CI) will be calculated using a Cochran-Mantel Haenszel (CMH) methodology stratified by the 3 stratification factors (age, PD-L1 status, and stage). The ORR difference between the 2 treatment arms with its 95% CI will be reported. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each randomized arm.
Time to Response and Duration of Response (per BICR)	Time to response (TTR) is defined as the time, in months, from randomization to the first objective documentation of PR or better assessed per BICR. Time to response is restricted to the population of participants who achieved a best response of PR or better assessed per BICR. Duration of objective response (DoR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) per BICR assessment, or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Participants who started any subsequent anticancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anticancer therapy. DoR will be evaluated for responders (ie, participants with confirmed CR or PR) only as assessed by BICR. The Kaplan-Meier method will be used to further summarize DOR, including DOR curves, medians with corresponding 95% CIs.
PFS, ORR, DoR, TTR per Investigator assessment of tumor imaging	See definition of endpoints above. Per Investigator assessment of tumor imaging according to RECIST 1.1. ORR, PFS, DOR, TTR assessed by investigator per RECIST 1.1 will be analyzed similarly to these endpoints assessed by BICR. No hypothesis testing will be performed.
Time to death or distant metastases (TTDM)	TTDM is defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the thorax (except for heart) according to RECIST 1.1, as assessed by the Investigator. Participants who have not developed distant metastasis or died at the time of analysis will be censored at the time of the latest date of assessment from their last RECIST 1.1 assessment. However, if the participant has distant metastasis or dies after 2 or more missed visits, the participant will be censored at the time of the latest RECIST 1.1 assessment prior to the 2 missed visits. If the participant has no visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline. TTDM will be analyzed similarly as primary time-to-event endpoints as PFS, OS. No hypothesis testing will be performed.
PFS on Next Line Therapy (PFS-2)	PFS on next-line therapy (PFS-2) is defined as the time from randomization to objectively documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurs first. Participants who were alive and without progression after the next line of therapy will be censored at last known alive date. PFS-2 will be analyzed similarly as primary time-to-event endpoints as PFS, OS. No hypothesis testing will be performed.

Endpoint	Statistical Analysis Methods
Patient-reported outcomes	Proportion without meaningful deterioration in symptoms: The proportion of participants with no meaningful deterioration in a disease-related symptom score (NSCLC-SAQ Total Score) by 48 weeks following initiation of maintenance treatment. A detailed description of analysis methods and the threshold for meaningful change will be provided in the statistical analysis plan (SAP).

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CCRT, concurrent chemoradiotherapy; CI, confidence interval; CMH, Cochran-Mantel Haenszel; CR, complete response; DoR, duration of response; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS-2, progression-free survival on next line therapy; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAP, statistical analysis plan; TTDM, time to death or distant metastases; TTR, time to response.

10.3.2 Safety Analyses

All safety analyses will be performed on all treated participants.

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	
Safety	Safety analysis will be performed in all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria. Frequency, management and resolution of IMAEs will be analyzed. A tabular summary and comparative analysis between treatment arms of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study treatment, dosing delays of the study treatment, corticosteroid details, re-challenge information and outcome of the AE are individually characterized: • pneumonitis IMAEs • diarrhea/colitis IMAEs • hepatitis IMAEs • nephritis and renal dysfunction IMAEs • rash IMAEs • endocrine IMAEs by subcategories including adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes
Exploratory	Will be described in the statistical analysis plan finalized before the first efficacy interim database lock.

Abbreviations: AE, adverse event; CTCAE v 4.0, Common Terminology Criteria for Adverse Events version 4.0; IMAE, immune-mediated adverse event; NCI, National Cancer Institute; SAE, serious adverse event.

10.3.3 Other Analyses

Additional information will be described in the statistical analysis plan.

Exploratory analyses for PK, IMG, healthcare resource utilization, PROs, and [redacted] will be described in the statistical analysis plan which will be finalized before the first efficacy interim database lock. The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

Additional psychometric analyses on the PRO measures will be described in a separate stand-alone PRO analysis plan.

10.3.4 Interim Analyses

Formal efficacy interim analyses for PFS and OS are planned for this study. An independent statistician external to BMS will perform these interim and final analyses. Table 10.3.4-1 gives an overview of schedule and timing.

Table 10.3.4-1: Interim Analyses Schedule

[redacted]

[redacted]

the formal planned efficacy interim analyses, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment during periodic safety reviews. However, no formal test will be performed and the study will not be stopped for the superiority during safety reviews. Additional details will be included in the DMC charter.

The Statistical Analysis Plan will further describe the planned interim analyses.

[redacted]

[redacted]

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
3DRT	3-dimensional radiotherapy
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cell
[redacted]	[redacted]
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTRO	American Society for Radiation Oncology
AUC	area under the concentration-time curve
Bcl-xL	B-cell lymphoma-extra large
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BTLA	B and T lymphocyte attenuator
BUN	blood urea nitrogen
C	cycle
Cavg28	average serum concentration at Day 28
CBC	complete blood count
CCRT	concurrent chemoradiotherapy
CD8	cluster of differentiation 8
CFR	Code of Federal Regulations

Term	Definition
CI	confidence interval
CK	creatine kinase
cm	centimeter
Cmax	maximum concentration
CMH	Cochran-Mantel Haenszel
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CT	computed tomography
CTCAE v 4.0	Common Terminology Criteria for Adverse Events version 4.0
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
D	day
DBL	database lock
DILI	drug induced liver injury
dL	deciliter
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
EBUS	endobronchial ultrasound
EC50	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eg	exempli gratia (for example)

Term	Definition
EGFR	epidermal growth factor receptor
EOI	end of infusion
EQ-5D-5L	5-level version of the EuroQol Group's EQ-5D
E-R	exposure-response
ESMO	European Society for Medical Oncology
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-L	Functional Assessment of Cancer Therapy – Lung Cancer
FEV1	forced expiratory volume during first second of forced breath
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
FWB	functional well-being
g	gram
G-CSF	granulocyte colony stimulating factors
[redacted]	[redacted]
GFR	glomerular filtration rate
GTV	gross tumor volume
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCRU	healthcare resource utilization
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator Brochure
IC50	half maximal inhibitory concentration
ICE	intercurrent event
ICF	informed consent form

Term	Definition
ICOS	inducible co-stimulator
ie	id est (that is)
IEC	independent ethics committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemical
IL	interleukin
IM	intramuscular
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal products
IMRT	intensity modulated radiotherapy
IO	immuno-oncology
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IU	international unit
IV	intravenous
kg	kilogram
L	liter
LA	locally advanced
LAR	legally acceptable representative
LCS	lung cancer subscale
LDH	lactate dehydrogenase
LFT	liver function test
mAB	monoclonal antibody
[redacted]	[redacted]
mg	milligram
min	minute

Term	Definition
mL	milliliter
mmHg	millimeters of mercury
MLR	mixed lymphocyte reaction
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
μg	microgram
N	number of participants or observations
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-small Cell Lung Cancer Symptom Assessment Questionnaire
OR	odds ratio
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical exam
PET	positron emission tomography
PFS	progression-free survival
PFS-2	progression-free survival on next line therapy
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response

Term	Definition
PRO	patient-reported outcome
Q12W	every 12 weeks
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QA	quality assurance
QC	quality control
R&D	Research and Development
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RT	reverse transcription
SAE	serious adverse event
sAG	surface antigen
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SmPC	Summary of Product Characteristics
SUSAR	suspected, unexpected serious adverse reaction
SWB	social/family well-being
T3	triiodothyronine
T4	thyroxine
TBP	treatment beyond progression
TCR	T cell receptor
TMB	tumor mutational burden
TNM	tumor nodal metastasis
TSH	thyroid stimulating hormone
TTDM	time to death or distant metastasis
TTR	time to response

Term	Definition
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VMAT	volumetric modulated arc therapy
vs	versus
WBC	white blood cell
[redacted]	
[redacted]	
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying Regulation EU No. 536/2014
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more participants of the trial or the scientific value of the trial.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to participants and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure

3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment, or according to local Product label requirements for individual chemotherapy agents, whichever is longer.*****

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

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

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

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment, or according to local Product label requirements for individual chemotherapy agents, whichever is longer.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant, or according to local Product label requirements for individual chemotherapy agents, whichever is longer.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment, or according to local Product label requirements for individual chemotherapy agents, whichever is longer.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment, or according to local Product label requirements for individual chemotherapy agents, whichever is longer.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 ECOG PERFORMANCE STATUS

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

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

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

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

For additional guidance on management of durvalumab-related toxicity, please refer to the approved Product Label for durvalumab.

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

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

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

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

GI Adverse Event Management Algorithm

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

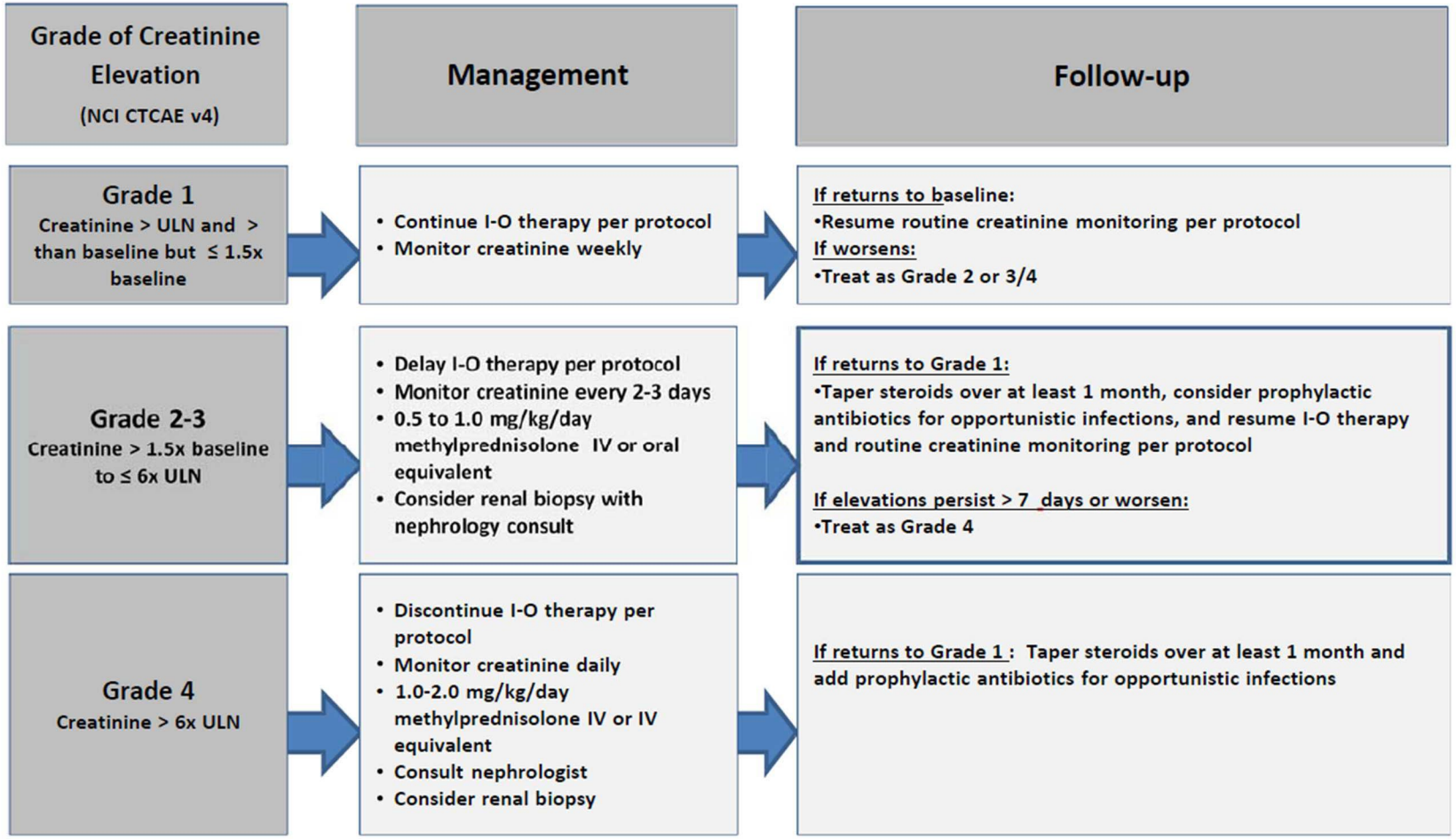
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

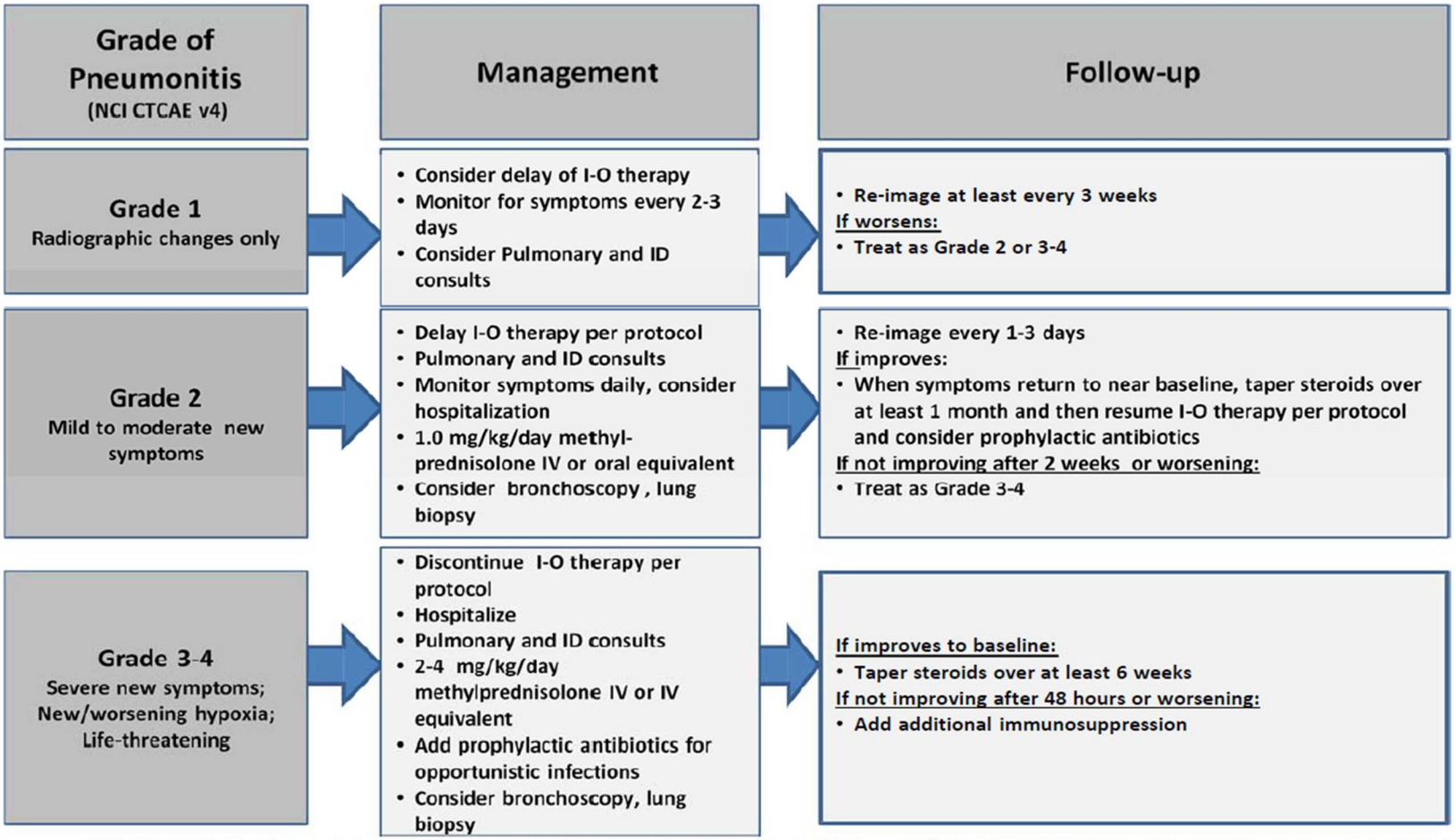


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

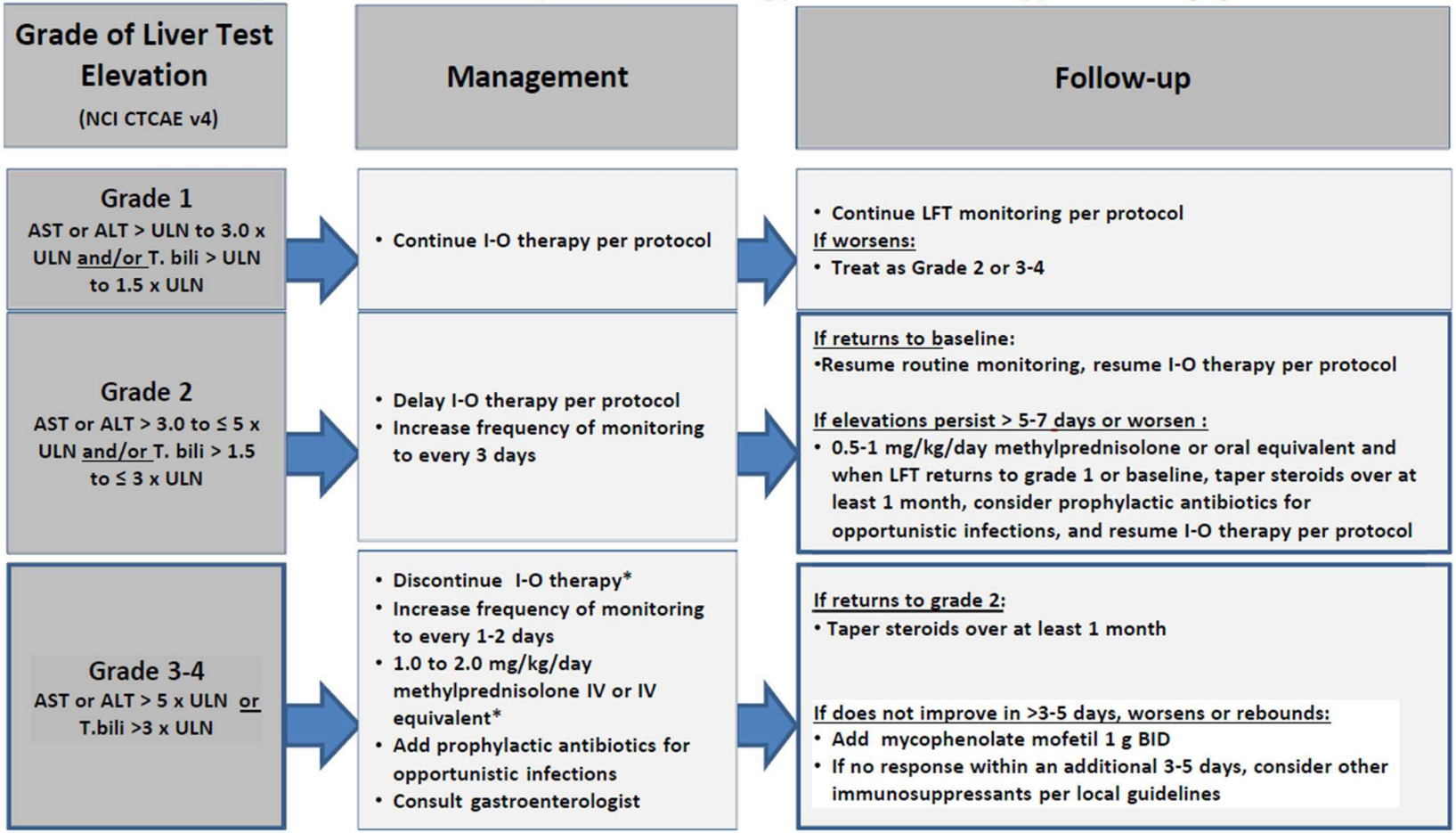


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



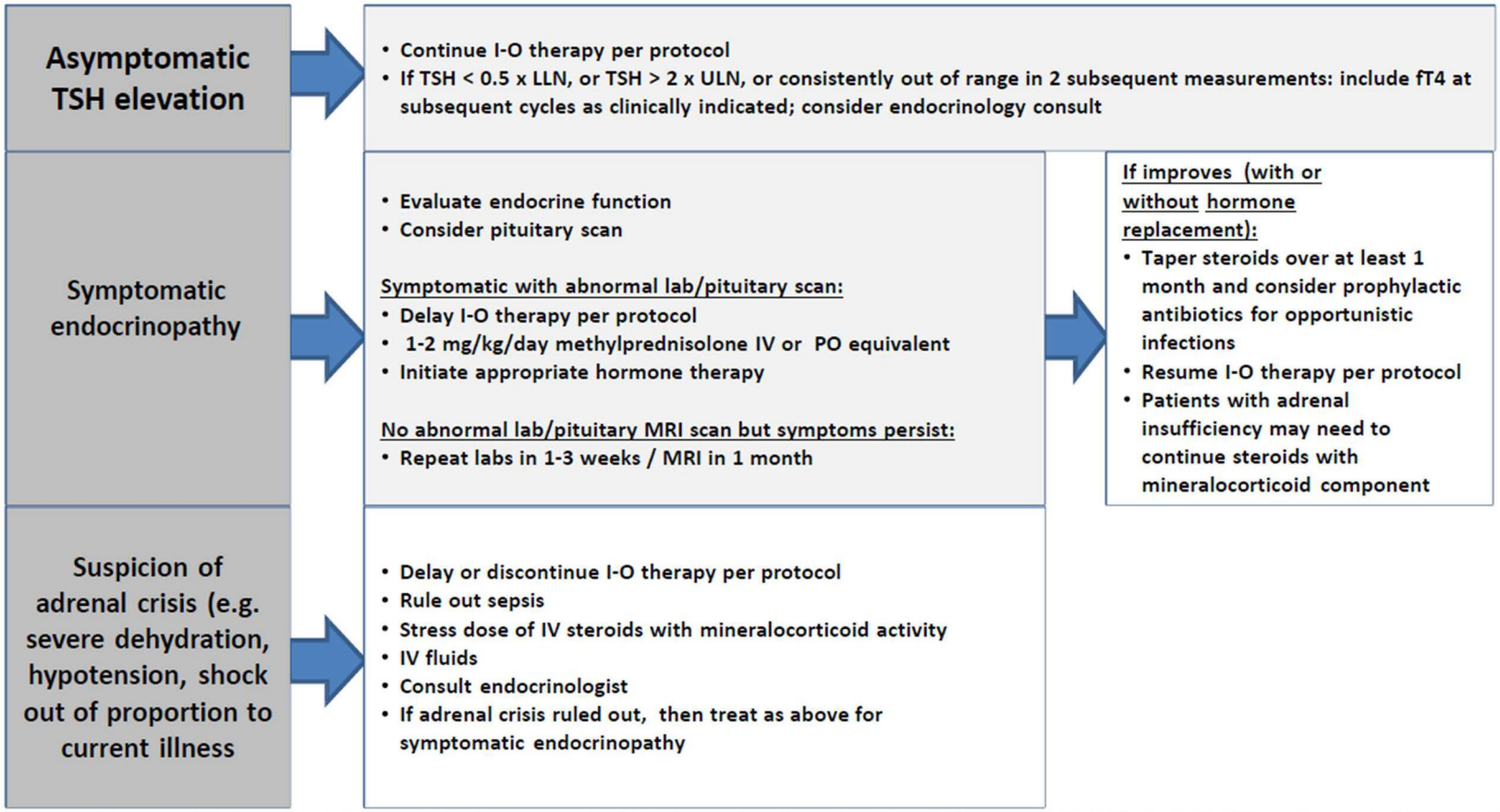
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

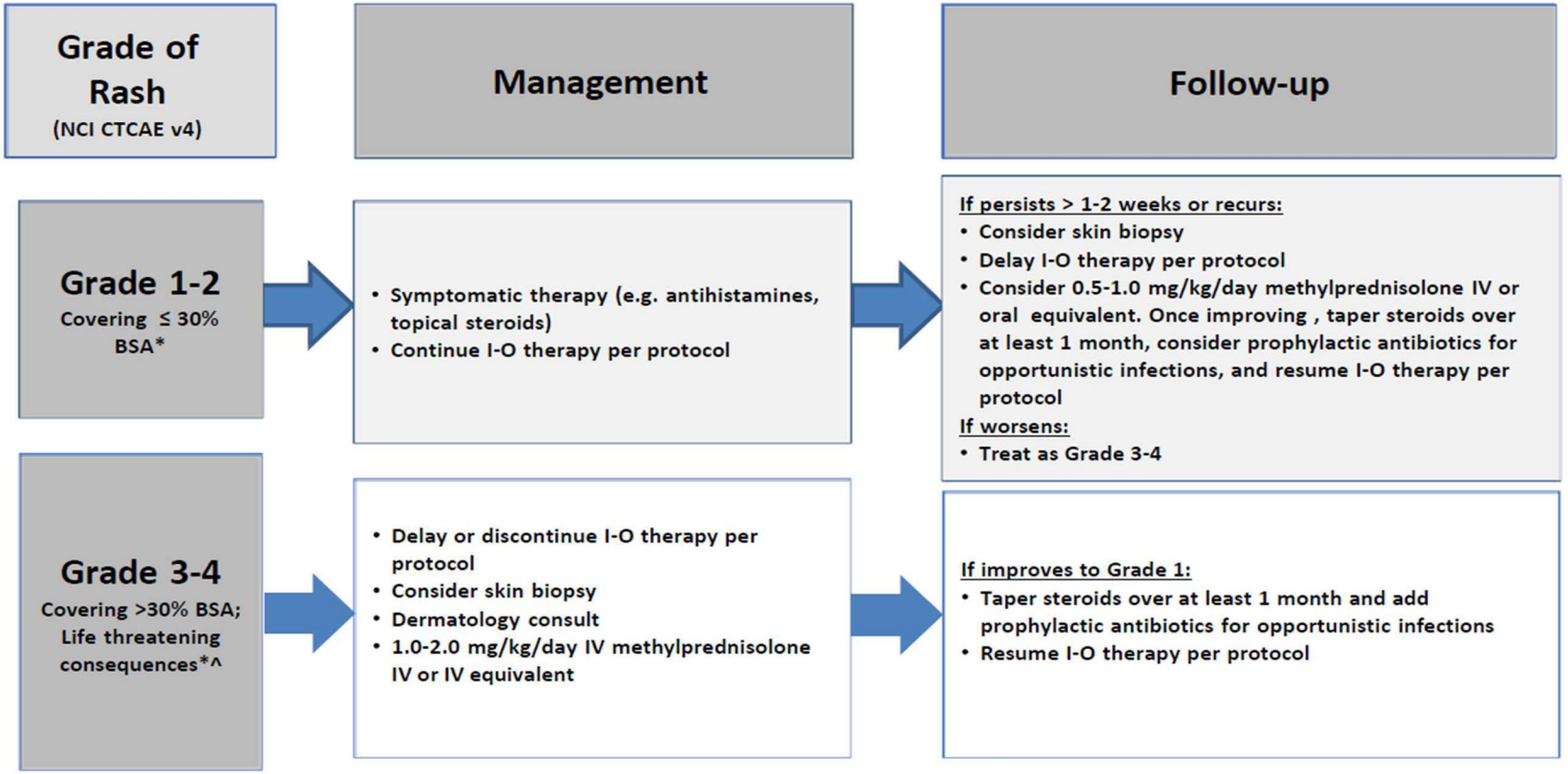


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

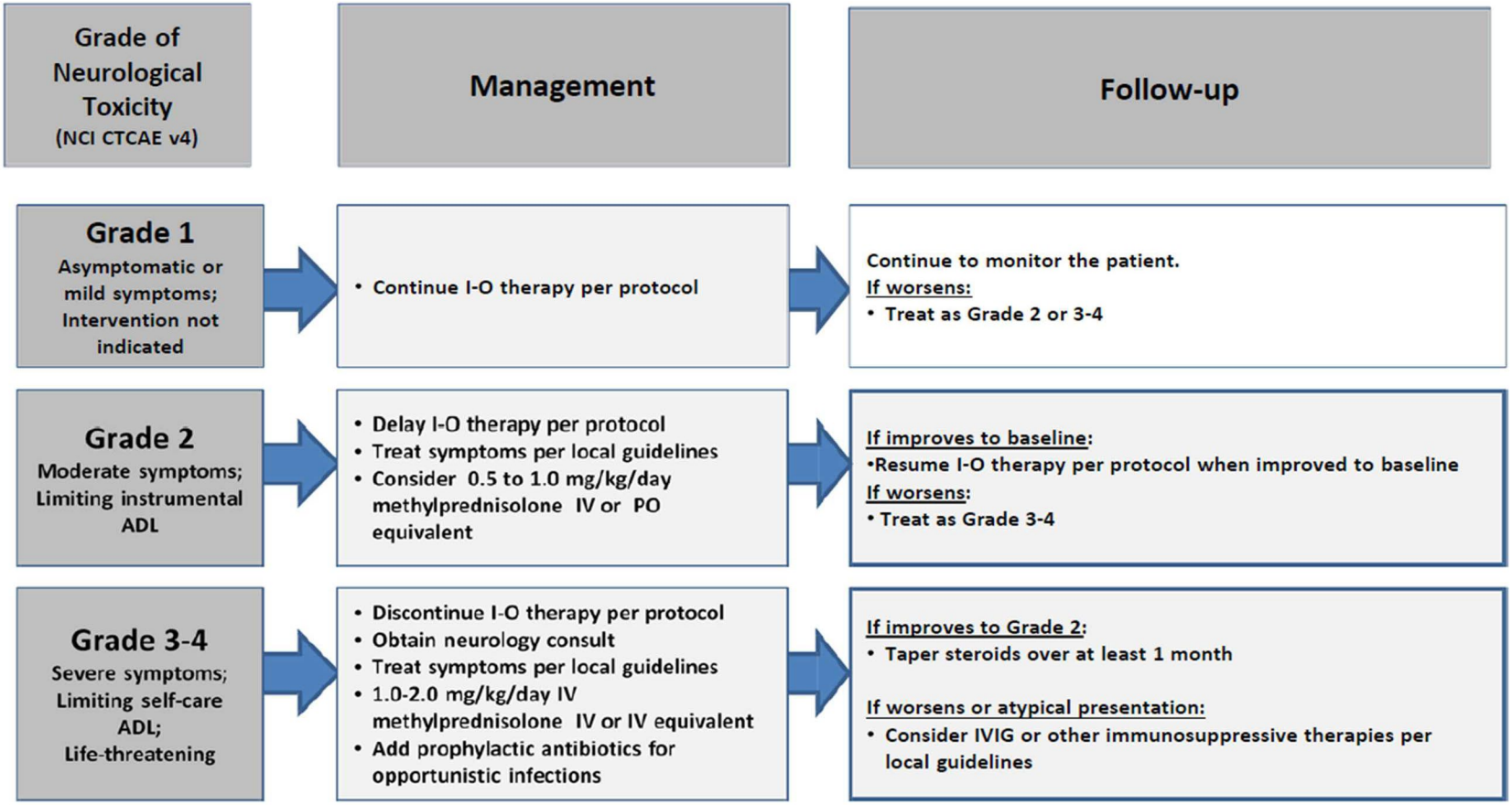
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

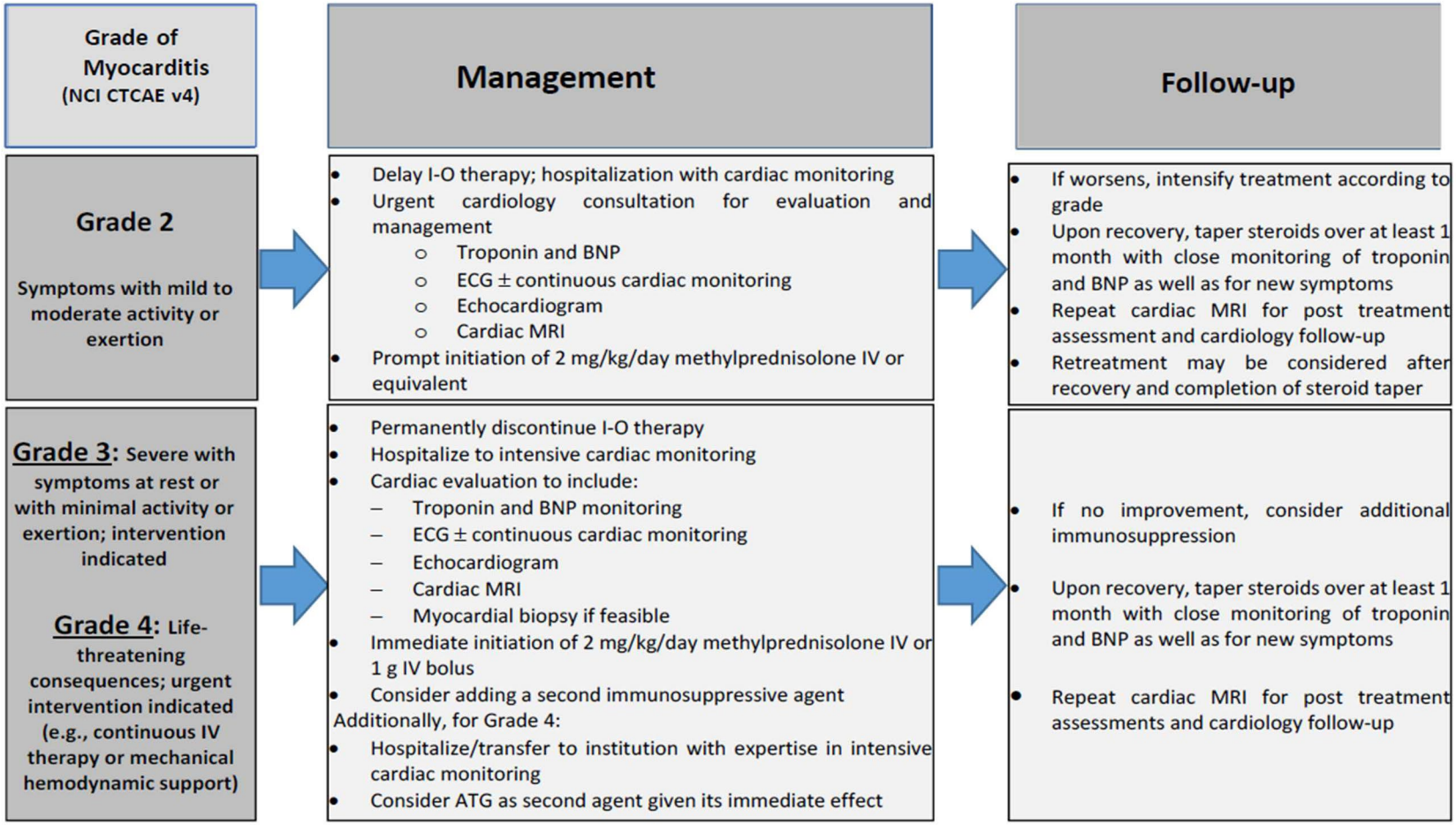
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

28–Sep–2020

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

28-Sep-2020

APPENDIX 7 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

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

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

2.3.3 Best Overall Response

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

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

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

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

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

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

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 8 SUMMARY OF RECOMMENDATIONS FOR NODAL GTV DELINEATION BASED ON FDG-PET–CT AND E(B)US-NA

When incidental nodal irradiation is low, such as with IMRT or VMAT, it is advised to add E(B)US-NA to FDG-PET–CT for mediastinal staging as it may:

- decrease geographical miss
- detect other benign reasons for PET-positivity
- confirm malignancy in PET-positive LN

Do NOT exclude LN that are PET-positive and E(B)US-negative from GTV as FN rate remains high (14%-16%), except if:

- a clear benign reason for PET-positivity is found at pathological examination e.g. anthracosilicosis or granulomatosis
- high suspicion of infection with symmetrical pattern and less FDG-avid compared with primary tumor; take into account clinical parameters
- negative pathology at E(B)US-NA is confirmed by mediastinoscopy

Select carefully which LN station to be sampled with E(B)US under local anesthesia:

- confirm malignancy or find benign etiology for PET-positivity
- sample “suspicious” PET-negative LN
- consider to discuss the selection of critical LN with endoscopist beforehand
- E(B)US should be performed after FDG-PET–CT scan to avoid FN PET-positive LN

Abbreviations: GTV = gross tumor volume; E(B)US-NA = endobronchial/esophageal ultrasound with needle aspiration; IMRT = intensity-modulated radiotherapy; VMAT = volumetric arc therapy; FN = false negative

SOURCE: Peeters ST, Dooms C, Van Baardwijk A, et al. Selective Mediastinal Node Irradiation in Non-Small Cell Lung Cancer in the Imrt/Vmat Era: How to Use E(B)Us-Na Information in Addition to Pet-Ct for Delineation? Radiother Oncol. 2016:120(2):273-8

APPENDIX 9 COUNTRY-SPECIFIC REQUIREMENTS FOR HIV TESTING

Argentina has additional requirements for exclusion of HIV positive participants and is locally mandated.

Original language	Country-specific language
Section 6.2.1 Exclusion Criteria for CCRT, Exclusion criterion 1 m)	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".
Table 9.4.4-1 Clinical Laboratory Assessments	Add: HIV at screening

Abbreviations: AIDS, acquired immunodeficiency syndrome; CCRT, concurrent chemoradiotherapy, HIV, human immunodeficiency virus.

APPENDIX 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 16-Aug-2021

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Global	Editorial changes (ie, grammar, punctuation, abbreviations, etc).	Improved readability. Minor, therefore have not been summarized.
Title Page	Updated contact name and role name. Study Director is now referred to as Clinical Scientist.	Change in study contact personnel.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated with changes in Section 2-10.	Consistency with main body of protocol.
2, Schedule of Activities; Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, Table 2-6, Table 2-7, and Table 2-8 6.2.1, Exclusion Criteria for CCRT 6.4.1, Retesting During Screening Period 7.4, Dosage Modification 9.2.1, Time Period and Frequency for Collecting AE and SAE Information 9.2.3, Follow-up of AEs and SAEs 9.8, Biomarkers; Table 9.8-1 [redacted]	Added language to the protocol for participants with suspected or confirmed SARS-CoV-2 infection. • [redacted] • AE/SAE language to all Section 2 tables and Section 9. • Criteria for exclusion from study, retesting, and dosage modification in Sections 6 and 7.	[redacted]
2, Schedule of Activities; Table 2-1 5.1.1, Screening Period 6.1.1, Inclusion Criteria for CCRT 9.8.1, Tumor Tissue Specimens	Updated protocol to change the number of unstained tumor tissue sections that may be submitted to central lab at screening from 15 to 5-10 and removed requirement to discuss inclusion with medical monitor if less than 15 slides are available. Updated Inclusion Criterion 2) e).	To address potential enrollment barriers.
2, Schedule of Activities; Table 2-1 5.1.1, Screening Period	1. Updated notes for Informed Consent row. 2. Updated notes for Pulmonary Function Tests row, and for Body Imaging row. Section 5.1.1 was updated to be consistent with Body Imaging notes.	1. Clarified timing of consent collection and requirement for re-consent and new participant number with re-enrollment. 2. Enlarged time window for pulmonary function tests and PET component to address real-world logistic challenges in scheduling these procedures and to avoid unnecessary radiation exposure to participants.
2, Schedule of Activities; Table 2-1 5.1.1, Screening Period 6.1.1, Inclusion Criteria for CCRT	Updated notes for Lymph Node Sampling row. Updated Inclusion Criterion 2) b). Updated text in Section 5.1.1.	Added text to account for cases in which T3N1 cannot be verified by biopsy due to the lesion being unamenable or procedure is medically infeasible and documentation of T3N1 status.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2, Schedule of Activities; Table 2-1, Table 2-2, Table 2-3, Table 2-5, Table 2-6, and Table 2-7	Added footnote a in Table 2-1, footnote c in Table 2-2 and Table 2-3, and footnote b in Table 2-5, Table 2-6, and Table 2-7.	Added footnote to address assessments for safety monitoring that may not be captured on CRF.
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-5, Table 2-6, Table 2-7, Table 2-9, and Table 2-10	Updated notes for Targeted Physical Examination, Weight, and Vital Signs (see also Targeted PE, Weight, and Vital Signs) row.	Clarified timing for weight assessment.
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-5, Table 2-6, and Table 2-7. Table 9.4.4-1 Clinical Safety Laboratory Assessments	Added row for Thyroid Stimulating Hormone (TSH) test. Updated text for TSH in Table 9.4.4-1.	To clarify that TSH test (with reflexive fT3 and fT4 if TSH is abnormal) is only required on Day 1 of every cycle (except for Arm C in the CCRT period only).
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-4, Table 2-5, Table 2-6, Table 2-7, Table 2-9, and Table 2-10	Updated notes for Pregnancy Test row updating timing of collection.	Updated and clarified timing of testing.
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-5, Table 2-6, and Table 2-7	Updated notes for Outcome Assessments.	Updated to address collection when dose is delayed.
2, Schedule of Activities; Table 2-2 7.1.4.2, Etoposide/cisplatin	Updated notes for Administer Etoposide row and text in Section 7.1.4.2.	To provide flexibility for dosing for Day 2 and 3.
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-5, Table 2-6, and Table 2-7	Added Body and/or Brain Imaging Row (Table 2-2 and Table 2-3). Footnote b added to Body Imaging row and Brain Imaging row (Table 2-4). Footnote d added to Body Imaging row and Brain Imaging row (Table 2-5, Table 2-6, Table 2-7, and Table 2-8).	Added to address the need for disease progression confirmation by BICR prior to subsequent therapy.
2, Schedule of Activities; Table 2-2, Table 2-3, Table 2-5, Table 2-6, Table 2-7, and Table 2-8 9.8, Biomarkers; Table 9.8-1 and [redacted] 9.8.1, Tumor Tissue Specimens	[redacted]	
2, Schedule of Activities; Table 2-2 and Table 2-3	Added footnote b to Cycle column headers.	Footnote added to address which procedures should and shouldn't be delayed when dose is delayed.
2, Schedule of Activities; Table 2-3	Removed Day 8 and Day 15 from Cycle 1.	Removed Days 8 and 15 of Cycle 1 as no assessments occur on those days.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2, Schedule of Activities; Table 2-3 7.1.4.1, Paclitaxel/Carboplatin Dosing	Updated notes for Administer Paclitaxel row, Administer Carboplatin row, and text in Section 7.1.4.1.	To provide flexibility for dosing for Day 8 and 15. Added note on premedication for clarity.
2, Schedule of Activities; Table 2-4	1. Updated notes for Body Imaging row. 2. Updated notes for Outcomes Assessments. 3. Updated footnote a.	1. Scan should be collected (not optional). 2. Outcome assessment notes were updated to specify collection at End of Recovery Visit. 3. Footnote updated to clarify collection of outcome assessments.
2, Schedule of Activities; Table 2-4, Table 2-5 and Table 2-6 5.1.3 , Recovery Period 5.1.4 , Maintenance Period 10.3.1 , Efficacy Analyses	In Table 2-4 (Recovery Period), removed the (± 7 days) in the column 2 header and updated notes for Body Imaging row. Updated footnote a in table and text in Sections 5.1.3 and 5.1.4. Updated Study Treatment row notes in Table 2-5 and Table 2-6 (Maintenance Period) to be consistent with Section 5.1.4. Section 10.3.1 PFS per BICR for A vs C statistical analyses methods were updated to be consistent with Section 2 and Section 5.	Clarified flexibility in timing of scheduled activities and duration in recovery period. Clarified flexibility in timing of maintenance treatment.
2, Schedule of Activities; Table 2-5, Table 2-6, and Table 2-7	Updated footnote a (Table 2-5, Table 2-6, and Table 2-7) and footnote b (Table 2-9 and Table 2-10).	Updated footnote as pregnancy testing should follow the testing schedule as described in table notes for pregnancy testing procedure.
2, Schedule of Activities, Table 2-6	Updated notes for Nivolumab Q4W.	Clarified timing between nivolumab doses.
2, Schedule of Activities; Table 2-7	Updated notes on the Durvalumab Q2W row.	Updated to include instructions for weight-based dosing.
2, Schedule of Activities; Table 2-8	Updated notes for Adverse Events Assessment (including SAEs) row.	Updated to include collection of drug-related adverse events beyond 100 days from last dose of study treatment.
2, Schedule of Activities; Table 2-9 and Table 2-10	Updated notes for Brain Imaging row.	Updated to make note consistent with body imaging notes.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
3, INTRODUCTION 3.3, Benefit/Risk Assessment 5.4.1, Rationale for Study Population and Study Comparator	Added sentence indicating that 4-year follow up data results were consistent with previously cited data.	Added updated data for durvalumab.
3.1.1, Research Hypothesis 4, OBJECTIVES AND ENDPOINTS 5.1, Overall Design; Figure 5.1-1 10.1, Sample Size Determination Figure 10.1-1 10.2, Populations for Analyses 10.3.1, Efficacy Analyses	Updated PFS assumptions and added OS for Arm A vs Arm C as a secondary objective. This includes updates for control arm assumption, delay effect, testing procedures, comparisons between arms, method of analysis descriptions.	To mitigate prolonged timing, OS is now a key secondary endpoint and will be tested hierarchically after PFS.
3.2.3, Clinical Experience with Nivolumab plus Ipilimumab Combination Therapy	Removed statement about DoR for CA209012. Updated safety data for CheckMate 227 and added data for CheckMate 9LA. Removed TMB data for CheckMate 227.	Added supporting information for use of nivolumab in combination with ipilimumab. Removed data that was not needed to support the combination therapy.
3.2.4, Clinical Experience with Nivolumab and CCRT 5.4.4, Rationale of Concurrent Scheduling of Nivolumab with CCRT 5.4.6, Rationale of Backbone CCRT	Updated text with data from Keynote 799.	Added supporting information for use of nivolumab in combination with CCRT.
3.3, Benefit/Risk Assessment 7.7.2, Prior and Concomitant Medications	Added text indicating non-live coronavirus disease 2019 (COVID-19) vaccinations will be considered a simple concomitant medication and handled in the same manner as other vaccines.	Current data suggests that non-live vaccine for COVID-19 will not negatively impact the benefit-risk for participants in this study.
4, OBJECTIVES AND ENDPOINTS	For secondary analysis of ORR, reference to CR rate has been removed.	ORR (CR+PR) is of primary interest and will be compared formally.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.2, CCRT Period 7.2, Method of Treatment Assignment	1. Added text in both sections for changes in actual vs planned CCRT regimen administration. 2. Text in Section 5.1.2 changed "should" to "must" for start of radiotherapy. 3. Added text to Section 5.1.2 to address cases of premature discontinuation of CCRT with reasons other than PD.	1. Change from Administrative Letter 03. To document and trace any change in CCRT treatment plan. 2. Added for clarity. 3. Added to allow participants to be considered for continuation into the recovery period with discussion between the Investigator and Medical Monitor.
5.1.8, Radiotherapy Quality Assurance and Quality Control	Removed sentence for real-time sampling of at least 20% of cases for review.	RT treatment plans for all participants will be reviewed by Quality, not just "at least 20%.".
5.4.1, Rationale for Study Population and Study Comparator	Removed background statistics for lung cancer and reordered text.	Sentence was removed to eliminate redundancy (text appears elsewhere in protocol) and paragraphs were reordered for flow/clarity.
5.5.1, Justification for Dosing Regimen of Nivolumab	Replaced text with updated data on nivolumab dosing, including exposure-response analyses.	Updated to include current supporting data for nivolumab dosing.
6, STUDY POPULATION	Added text excluding protocol waivers/exemptions.	Clarified that study will not approve protocol deviations to enrollment criteria.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1.1, Inclusion Criteria for CCRT 9.2, Adverse Events	1. Updated Inclusion Criterion 1) a) and Section 9.2. 2. Updated Inclusion Criterion 2) b). 3. Added sub criteria i) through iii) to Inclusion Criterion 3 b), added sub criteria i) and sub-sub criteria (1) and (2) to Inclusion Criterion d), and updated Inclusion Criterion 3) f) and added sub-criteria i) and ii) to 3) f).	1. Changed from authorized to acceptable representative to be consistent with text in Appendix 2. For inclusion criteria, text in parentheses was added based on feedback from [redacted] 2. Clarified both histology and cytology are acceptable for disease diagnosis. Clarified patients medically unfit for general anesthesia/surgery are not eligible as intensive study multi-modality regimens may be unsafe for such patients. Clarified vertebral invasion must not extend into spinal cord as it is unlikely to comply with radiation dose constraints. 3. Updated to include more information and guidance on the testing, counseling, and monitoring of women of childbearing potential (WOCBP), male partners of WOCBP, and contraceptive methods.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.3 Recovery Period 6.1.2, Inclusion Criteria for Maintenance Treatment	1. Removed last sentence in the first paragraph in 5.1.3. 2. Removed Inclusion Criterion 4) a). 3. Updated Inclusion Criterion 4) b). 4. Updated Inclusion Criterion 4) d).	1. Removed disease progression as assessed by investigator to keep consistent with updates in Inclusion Criterion 4) b) in Section 6.1.2. 2. Removed to eliminate potential eligibility barriers into the maintenance period and allow for investigator's discretion. 3. Clarified that absence of progressive disease must be confirmed by BICR. 4. Esophagitis added to be consistent with guidance in other section of protocol. Additional text added to provide flexibility for inclusion of participants in maintenance treatment.
6.2.1, Exclusion Criteria for CCRT 7.7.1, Prohibited and/or Restricted Treatments	1. Updated Exclusion Criterion 1) c). 2. Added Exclusion Criterion 1) n). 3. Updated botanical preparations to complementary medications in Exclusion Criterion 2) d) and in Section 7.7.1. 4. Updated Exclusion Criterion 2) a). 5. Added Exclusion Criterion 2, g). 6. Updated Exclusion Criterion 3) i).	1. Updated criterion to eliminate potential unnecessary enrollment barriers. 2. Added exclusion for participants with SARS-CoV-2 infection within 4 weeks of screening to avoid placing participants at higher risk of adverse events when receiving study treatment. 3. To prohibit both botanical and nonbotanical preparations used to treat the disease under study or as supportive care. 4. Clarified exceptions for prior thoracic therapy to address enrollment barrier. 5. Added criterion for prior/current treatment in interventional trials. 6. Updated to emphasize that both FEV1 and DLCO is required for eligibility.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.2.2, Exclusion Criteria for Maintenance	Added text for delay between recovery and maintenance period.	Clarified eligibility/procedure if recovery period is delayed.
6.4.1, Retesting During Screening Period	Added text addressing re-enrollment and participant number.	Clarified that re-enrolled participants should receive a new participant number.
7, TREATMENT; Table 7-1	1. Added additional row and footnote a (this caused the prior footnotes to become b and c) and updated footnote c. 2. Added a note indicating that radiotherapy is not considered study treatment.	1. 50 mg ipilimumab vial presentation will be available starting Q3 2022 and 200 mg vials are being phased out. Footnote c change from Administrative Letter 03. 2. To clarify that radiotherapy is background treatment.
7.1.1, Nivolumab Dosing	Updated text to include "approximately" before infusion time. Added text for flushing the IV line, order of infusion, and reminder to assure sterility of prepared solution.	Added instruction to ensure full delivery of nivolumab dose. Clarified order of administration of study treatment when used in combination. Added additional details for the safe storage, preparation, and administration of nivolumab.
7.1.2, Ipilimumab Dosing	Updated text to include "approximately" before infusion time. Updated text to note that dosing visits cannot be skipped. Added text to use separate infusion bags and filters when administering nivolumab and ipilimumab on the same day.	Added instruction to ensure full delivery of nivolumab dose. Clarified that ipilimumab doses cannot be skipped. Added additional details for the safe storage, preparation, and administration of ipilimumab.
7.1.4.1 , Paclitaxel/Carboplatin Dosing 7.1.4.2 , Etoposide/cisplatin 7.1.4.3 , Pemetrexed/cisplatin 7.1.4.4 , Carboplatin Dosing (with Etoposide or Pemetrexed)	Where applicable, "local label requirements" has been changed to "local standard."	Administrative change.
7.1.4.2, Etoposide/cisplatin	Deleted sentence for BSA.	Changed to accommodate varying regional practice/clinical standards.
7.1.5, Radiotherapy Planning and Delivery	Added texted referring back to the Thoracic Radiotherapy Guidelines.	Added per feedback [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.4.1.1, Criteria to Resume Nivolumab	1. Added criteria to resume treatment. 2. Updated sentence for adrenal insufficiency.	1. Added to highlight that study treatment can be resumed after AE management is complete. 2. Administrative change.
7.4.5, Chemotherapy Dose Delay, Dose Modification, and Criteria to Resume Treatment	Added text that modifications of chemotherapy dose should follow approved product labeling in addition to local institutional standards.	Changed to accommodate local labeling and clinical standards for the safe dosing and administration of chemotherapy.
7.4.5, Chemotherapy Dose Delay, Dose Modification, and Criteria to Resume Treatment 7.7.1, Prohibited and/or Restricted Treatments	Added text for administration of growth colony stimulating factors (GCSF) for supporter measures.	Clarified GCSFs can be administered and should only be used to support hematologic recovery.
7.4.5.7, Dose Modifications for Toxicities with Carboplatin + Paclitaxel Regimen	Qualified statement that there are no dose reductions.	Changed to accommodate varying regional practice/clinical standards.
8.1, Discontinuation from Study Treatment	Text updated to say that discontinuation must be document in the participant's medical records per local regulatory requirements in each region/country.	Changed to accommodate varying regional practice/clinical standards.
8.1.4, Discontinuation Criteria for Chemoradiotherapy	In the fifth bullet, the dose reduction for etoposide was changed to 25% when substituting for pemetrexed.	Corrected typo from Revised Protocol 01.
9.1.1, Imaging Assessment for the Study	Changed "will" to "must." Expanded language for scans done at other time points.	Text changed for emphasis. Expanded language specifically calls out scans at unscheduled time points and outside institutions.
9.1.2, Outcomes Research Assessments	Added text indicating measures should be entered into the CRF and allowing alternative administration methods if needed.	Clarified recording of PRO measures in long-term follow-up period. Added flexibility to data collection if circumstances require alternative methods of collection.
9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Removed first sentence about location of Reference Safety Information in IB. Added text for collection of non-serious adverse events (AEs) and serious adverse events (SAEs) for randomized but never-treated participants.	Sentence no longer reflects the appropriate location in the IB for Reference Safety Information. Updated section to reflect all the AE information to be collected and the collection timing.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.2.2, Method of Detecting AEs and SAEs	Added text for assessment/collection of immune-mediated AEs.	Updated instructions for collection of safety data (adverse events).
9.5, Pharmacokinetics; Table 9.5-1 to Table 9.5-4	Updated footnote a and b.	Clarified definition of end of infusion-PK and need for full infusion of study treatment prior to sample collection.
9.8, Biomarkers; Table 9.8-1 to [redacted]	[redacted] 2. Updated footnote a.	[redacted] 2. Updated based on local country-specific restrictions.
9.8 Biomarkers; Table 9.8-1	Added footnote d.	[redacted]
9.8 , Biomarkers; [redacted]	[redacted]	Removed based on the biomarker requirement review.
9.8.1 , Tumor Tissue Specimens	Added text that specifies there should be no intervening therapy between tumor sample collection and randomization and for possible uses for screening and progression tumor samples.	Added for clarity.
[redacted]		
[redacted]	[redacted]	Administrative change.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	Updated for clarity.
10.3 , Statistical Analyses 10.3.1 , Efficacy Analyses	1. Added general text for summary of continuous and categorical data. 2. Updated analyses description for PFS, TTR/DoR, investigator-assessed efficacy endpoints, TTDM, PFS-2, and patient-reported outcomes.	1. Made text more general to cover all the data being collected and not just the PFS and OS data described previously. 2. Clarified the statistical analysis methods used and aligned definition of primary PFS analysis with that in PACIFIC and per ITT principles in ICH E9 (R1) addendum. This intends to mitigate the impact of non-administrative censoring seen in external NSCLC trials, which was not previously accounted for in the CA20973L analysis plan.
10.1.1, Sample Size Justification for PFS	Updated PFS assumptions of control arm. [redacted]	To incorporate most recent PACIFIC and PROCLAIM updated PFS assumptions for the control arm.
10.1.2, Sample Size Justification for OS	[redacted] Added additional OS interims based on timing of PFS interims.	OS assumptions and timing of analyses are adjusted following updated PFS.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
10.3.3, Other Analyses	Reordered first sentence and indicated when information in the Statistical Analysis Plan will be finalized.	Updated text to clarify that all the analyses listed in this section are exploratory and that the analysis plan will be finalized at database lock and unblinding.
10.3.4, Interim Analyses	Updated text to make a tabular schedule for interim analyses based on updated assumptions outlined in Section 10.1.	Updated PFS and OS assumptions.
Appendix 2	Updated language under Monitoring subsection. Added Dissemination of Clinical Study Data subsection.	To allow alternative monitoring in circumstances where on-site monitoring is not advised.
Appendix 6	Minor noncontent-related update to the approval date on the management algorithms (lower right corner).	Updated to reflect their inclusion in nivolumab IB addendum 01
Appendix 9	Updated the applicable countries.	Removed Spain as mandatory HIV test at screening is no more applicable in Spain. Removed Czech Republic as it has not participated in the trial.

Overall rationale for Revised Protocol 01, 04-Mar-2020

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis Section 4 Objectives and Endpoints	Updated language for objectives and endpoints	Description of objectives updated to more succinctly characterize comparisons of different treatment arms and overall study endpoints
Synopsis Section 5 Study Design Section 7.2 Method of Treatment Assignment	Revised PD-L1 stratification to include 3 separate PD-L1 stratification: ≥1%, <1%, and indeterminate or not evaluable	Update made based on [redacted] feedback
Table 2-1 Screening Section 5.1.1 Screening Period	Instructions added for lymph node sampling for cT4 disease and PET/CT body imaging.	Additional instructions provide clarity for data collection.
Synopsis Table 2-2 CCRT Period Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Section 5.1 Overall Design Section 5.1.2 CCRT Period Section 7.1.5 Radiotherapy Planning and Delivery	Instructions added for participants who skip Cycle 1 of CCRT compared to participants who receive Cycle 1 therapy.	Additional instructions provide clarity for data collection.
Synopsis Table 2-2 CCRT Period Cisplatin (or Carboplatin) + Etoposide or Pemetrexed Table 2-3 CCRT Period Carboplatin and Paclitaxel Section 5.1.2 CCRT Period Table 7-1 Study treatments for CA20973L Section 7.1.4 Chemotherapy Dosing Section 7.4.5 Chemotherapy Dose Delay, Dose Modification, and Criteria to Resume Treatment Section 7.4.5.5 Dose Modifications for Toxicities with Carboplatin + Paclitaxel Regimen Table 7.4.5.5-1 Carboplatin + Paclitaxel Dose Modifications for Hematological Toxicities	Additional chemotherapy regimen (carboplatin + paclitaxel) and table added Instructions added for chemotherapy pre-specification and administration	Carboplatin + paclitaxel regimen added to align treatment options in the trial with global standard of care. Additional instructions provide clarity for treatment pre-specification, administration and data collection.
Table 2-2 Concurrent CCRT Period Cisplatin (or Carboplatin) + Etoposide or Pemetrexed	Instructions added for timing and coordination of radiotherapy	Additional instructions provide clarity for data collection.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.2.3 Clinical Experience with Nivolumab plus Ipilimumab Combination Therapy Section 3.2.4 Clinical Experience with Nivolumab and CCRT Section 5.4.1 Rationale for Study Population and Study Comparator Section 5.4.4 Rationale of Concurrent Scheduling of Nivolumab with CCRT Section 5.4.6 Rationale of Backbone CCRT	Updated clinical background of ongoing clinical studies using same drug treatments and/or CCRT.	Additional information provide clarity to characterize risk/benefit of study.
Section 6.1 Study Population Inclusion Criteria	Inclusion criteria was updated to include: • Participant's legal authorized representative may sign the approved ICF on behalf of participant • Participants must be evaluated by the site's multidisciplinary team (eg, medical oncologist, surgeon, radiologist) during screening to assess the suitability of the participant for the study. • Adherence to local product label contraception requirements for chemotherapy	[redacted] request Given the multidisciplinary nature of treating patients with stage III NSCLC, evaluating the suitability of a participant for the trial within the multidisciplinary team ensures that the study is in the best interest of the participant [redacted] request to account for labeling of chemotherapy agents To provide flexibility for clinical discretion of the Investigator

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Study Population Exclusion Criteria for Maintenance	Radiotherapy dose constraints relaxed for eligibility purposes Exclusion criteria was updated for hearing loss, neuropathy Participants with myelosuppression may be allowed to proceed with maintenance therapy at the investigator's discretion	Radiotherapy planning may not be complete at time of eligibility assessment during Screening. Radiotherapy dose constraints are now specified in the separate radiotherapy guidelines document Criteria for hearing loss and neuropathy will adhere to local product label. Following CCRT, it may take longer than 42 days for hematological values to recover, while a participant is in suitable health to continue with maintenance IO therapy. Flexibility permitted per investigator's clinical judgement of hematological values.
Section 7.4.4.1 Management Algorithms for Ipilimumab, Nivolumab, or Durvalumab	Updated algorithms for myocarditis	Updated algorithms for myocarditis
Table 9.4.4-1 Clinical Safety Laboratory Assessments	Removed amylase and lipase collection	Align clinical laboratory assessments with nivolumab program standards
Table 9.5-1 Pharmacokinetic and Immunogenicity Sampling in Arm A (CCRT) Table 9.5-3 Pharmacokinetic and Immunogenicity Sampling in Arm B (CCRT)	Cycle 2 Day 1 EOI sampling added	Allows for consistency in PK and IMG sample collection for participants who initiate treatment at Cycle 1 of CCRT and participants who initiate treatment at Cycle 2
[redacted]		
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized