Official Title of Study:

A Phase 3, Randomized, Double-blind Study of Neoadjuvant Chemotherapy plus Nivolumab versus Neoadjuvant Chemotherapy plus Placebo, followed by Surgical Resection and Adjuvant Treatment with Nivolumab or Placebo for Participants with Resectable Stage II-IIIB Non-small Cell Lung Cancer

(CheckMate 77T, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 77T)

Protocol: CA209-77T

NCT Number: NCT04025879

Document Date (Date in which document was last revised): 28-Feb-2024

Protocol Number: CA20977T
IND Number: 100,052
EU CT Number: 2022-502658-15
NCT Number NCT04025879
Universal Trial Number U1111-1226-5321
Date: 26-Mar-2019
Revised date 28-Feb-2024

CLINICAL PROTOCOL CA20977T

A Phase 3, Randomized, Double-blind Study of Neoadjuvant Chemotherapy plus Nivolumab versus Neoadjuvant Chemotherapy plus Placebo, followed by Surgical Resection and Adjuvant Treatment with Nivolumab or Placebo for Participants with Resectable Stage II-IIIB Non-small Cell Lung Cancer

(CheckMate 77T, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 77T)

Short title: A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy plus Placebo, Followed by Surgical Removal and Adjuvant Treatment with Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer

Protocol Amendment 04

Incorporates Administrative Letters 04 and 06

[redacted] **Medical Monitor**
Route de Perreux 1, 2017
Switzerland
Phone: [redacted]
Email: [redacted]

[redacted]
3401 Princeton Pike
Lawrenceville, NJ 08648
Telephone (office): [redacted]
Email: [redacted]

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

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

organization will participate in and/or the performance of the proposed BMS sponsored study. Any permitted disclosures will be made only on a confidential "need to know" basis within your organization or to your independent ethics committee(s). Any other use, copying, disclosure or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information (eg, amendments) that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	28-Feb-2024	The primary reasons for this amendment are to: • Clarify the timing of the imaging requirements • Reduce the number of sample collections for circulating tumor deoxyribonucleic acid • Update the contraceptive requirements to align with the current approved product label.
Administrative Letter 06	01-Dec-2022	Updated study personnel information.
Administrative Letter 05	25-Aug-2021	Updated study personnel information.
Administrative Letter 04	10-May-2021	Corrected a typo found in Table 9.8.1-1 in protocol amendment 03.
Protocol Amendment 03	20-Apr-2021	• Updated requirement for tumor tissue submission at screening, and upon progression or recurrence of disease • Language regarding event-free survival was aligned throughout the document • Imaging requirements and definitions were clarified for the neoadjuvant setting • SARS-CoV-2 serology samples added • AE/SAE collection added to collect SARS-CoV-2 related events.
Revised Protocol 02	11-May-2020	• Updated PD-L1 stratification • Clarified language for inclusion criteria for tumor eligibility • Updated Table 2-4 survival status window and collection of EQ-5D-3L outcomes by phone • Updated window for preoperative imaging assessment • Clarifies instructions when participants do not receive surgery • Removed carboplatin + docetaxel as a chemotherapy regimen for patients with squamous histology • Added CYP3A4 inhibitors as prohibited medications when treated with docetaxel • Added docetaxel dose reduction for impaired renal function • Added docetaxel treatment delay when total bilirubin > ULN • Added docetaxel discontinuation for cystoid macular edema
Revised Protocol 01	20-Dec-2019	[redacted] the revised protocol: • modifies endpoints and definitions • adds additional chemotherapy regimens • instructs participants to follow local regulations for pregnancy testing and contraceptive use. • incorporates Administrative Letter 01 Additional updates were made to the imaging assessments and biomarker collections.

Document	Date of Issue	Summary of Change
Original Protocol	26-Mar-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

The primary reasons for this amendment are to:

- Clarify the timing of the imaging requirements
- Reduce the number of sample collections for circulating tumor deoxyribonucleic acid (ctDNA)
- Update the contraceptive requirements to align with the current approved product label.

Additional revisions, including to the Synopsis, have been made to align the protocol with respect to these changes.

This amendment incorporates the changes from the approved Administrative Letters 04 and 06 which are detailed in the Document History but not listed in the Summary of Key changes below.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated EudraCT Number to European Union (EU) Clinical Trial (CT) Number.	The term "EudraCT" is obsolete, as it refers to the previous legislation shortening the number per clinical trial regulation minimum requirements.
	Updated Clinical Scientist contact information.	To reflect current contact information.
Table 2-3: Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments (CA20977T) Table 2-4: Long-term Follow-up Assessments (CA20977T)	Updated timing of body imaging.	Timing of imaging requirements was clarified throughout the protocol. There are no changes to how this data is collected, just clarifying previously unclear information.
Section 5.1.2.5: Post surgical/Preadjuvant Evaluation Section 9.1.2.1: Neodadjuvant and Pre-Surgical Imaging Section 9.1.2.2: Post Surgical / Preadjuvant Restaging and Adjuvant Imaging Section 9.1.2.4: BICR Assessment of Progression	Added that, in addition, scans will continue until investigator-assessed distant metastasis.	Clarified requirement of imaging assessments from the time of local/locoregional recurrence until distant metastasis.
Figure 5.1-1: CA20977T Schema	Removed “and follow-up” from Biomarker collection and added that Follow-up is for up to “and including” 5 years from randomization.	For consistency with changes in the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Figure 5.1.2-1: CA20977T Flowchart for Efficacy and Safety Data Collection Table 9.8.1-1: Biomarker Sample Schedule for All Participants	Removed ctDNA collections from Year 2 and Year 3 and added a footnote "b" to Table 9.8.1-1. Plasma ctDNA samples should only be collected during Years 2 through 5 at the time of recurrence or progression.	To clarify ctDNA sample collection timing and to reduce the number of collections to reduce patient burden.
Section 9.2.5: Pregnancy Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated contraception and reporting requirements.	To align with the current approved product label.
Table 9.4.4-1: Clinical Laboratory Assessments	Removed "pre" from "Hepatitis B/C, pre-screening only" and "Follicle stimulating hormone pre-screening only."	To align with current protocol requirement.
Table 9.8.1-1: Biomarker Sample Schedule for All Participants	Removed footnote from Surgery/Resection row regarding participants stopping treatment for reasons other than blinded independent central review confirmed disease progression or recurrence during Adjuvant Treatment Period.	Administrative change to reduce confusion.
Appendix 2: Study Governance Considerations	Added Dissemination of Clinical Study Data section.	Updated based on BMS policy for dissemination of study data.
Throughout	Editorial updates.	Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Double-blind Study of Neoadjuvant Chemotherapy plus Nivolumab versus Neoadjuvant Chemotherapy plus Placebo, followed by Surgical Resection and Adjuvant Treatment with Nivolumab or Placebo for Participants with Resectable Stage II-IIIB Non-small Cell Lung Cancer

(CheckMate 77T, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 77T)

Short title: A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy plus Placebo, Followed by Surgical Removal and Adjuvant Treatment with Nivolumab or Placebo for Participants with Surgically Removable Early Stage Non-Small Cell Lung Cancer

Study Phase: 3

Rationale: Approximately 80% of lung cancer cases are NSCLC, with most patients presenting with late stage disease. Of these patients with NSCLC, 20% present with stage I or II disease, whereas 30% present with stage III disease and 50% with stage IV disease. Patients with pathologic stage I NSCLC have a 5-year survival of approximately 60%. Stage II to III NSCLC patients have a 5-year survival of approximately 25% to 40%.[1] The early-stage (II-IIIB) NSCLC represents a population of high unmet need with poor 5-year survival.

Surgical resection remains the mainstay of treatment for Stage I and II patients. Despite potential curative surgery, approximately 50% of stage IB and 60-75% of stage I-II NSCLC patients will relapse and eventually die of their disease.[2,3] A rational approach to improve survival in these patients is to eradicate micrometastatic disease and to minimize the risk of relapse with adjuvant or neoadjuvant chemotherapy. This periadjuvant phase 3 study (CA20977T) will evaluate the clinical efficacy and will establish the safety of neoadjuvant therapy of nivolumab plus platinum-based doublet chemotherapy followed by adjuvant therapy of nivolumab in resectable lung cancer.

Study Population: Participants with resectable Stage IIA >4 cm - IIIB (T3N2) non-small cell lung cancer

Objectives and Endpoints:

Table 1-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the event-free survival (EFS) by blinded independent central review (BICR) in Arm A vs Arm B participants	• EFS is defined as the length of time from randomization to any of the following events: progression of disease or worsening of disease precluding surgery, if surgery is attempted but gross resection is abandoned due to unresectable tumor or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due

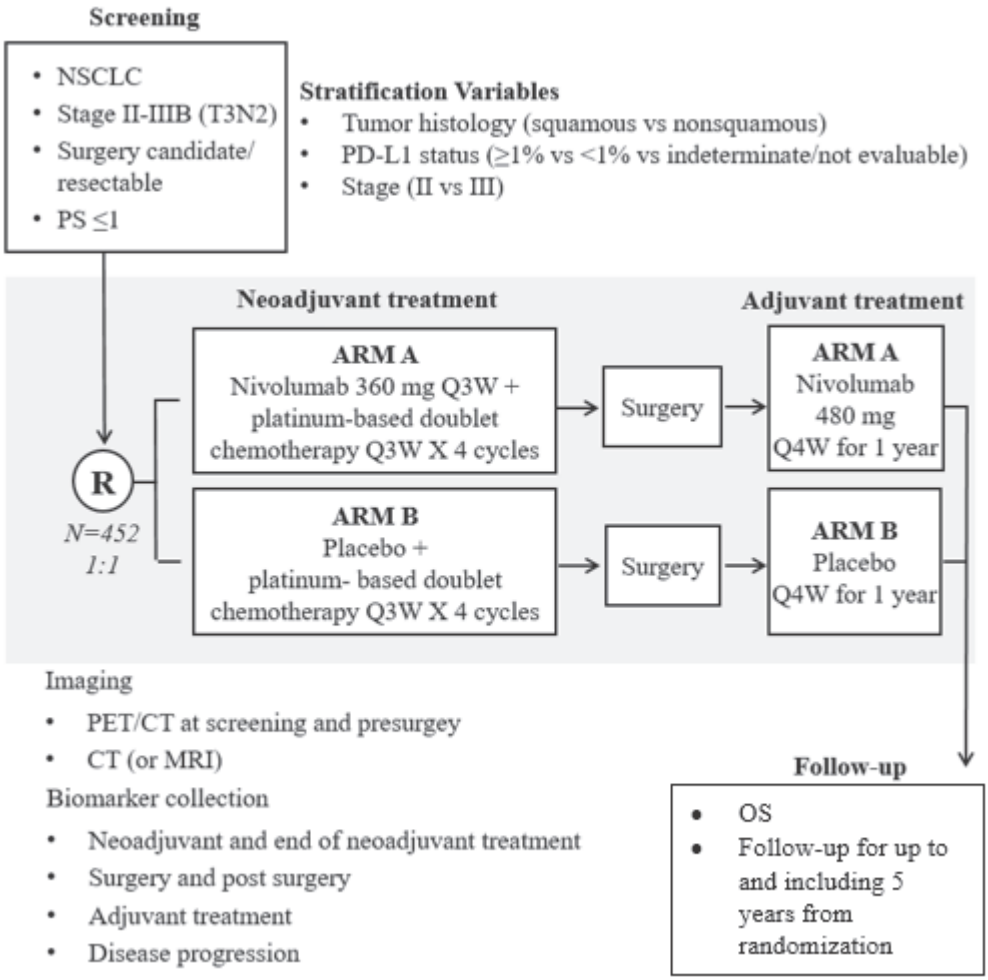
Table 1-1: Objectives and Endpoints	
Objectives	**Endpoints**
	to any cause. Progression/recurrence will be assessed by BICR per RECIST 1.1. • Participants who do not undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 progression or death.
Secondary	
• To compare the overall survival (OS) in Arm A vs Arm B participants	• 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 subject was known to be alive.
• To assess the pathologic complete response (pCR) rate by BIPR in Arm A vs Arm B participants	• pCR rate is defined as the number of randomized participants with absence of residual viable tumor in lung and lymph nodes as evaluated by blinded independent pathology review (BIPR), divided by the number of randomized participants for each treatment group.
• To assess the major pathological response (MPR) rate by BIPR in Arm A vs Arm B participants	• MPR rate is defined as number of randomized participants with ≤10% residual viable tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group.
• To assess safety and tolerability in Arm A vs Arm B participants	• Incidence of AEs, SAEs, and select AEs

Overall Design:

This phase 3, double-blind, periadjuvant study (CA20977T) will evaluate the clinical efficacy and will establish the safety of neoadjuvant therapy of nivolumab plus platinum-based doublet chemotherapy followed by adjuvant therapy of nivolumab in resectable lung cancer.

Number of Participants: Approximately 452 participants

Schema for CA20977T



Treatment Arms and Duration:

- **Arm A**: nivolumab 360 mg Q3W + SOC platinum-based doublet chemotherapy Q3W x 4 cycles as neoadjuvant treatment followed by surgery; then post surgery, nivolumab 480 mg Q4W adjuvant therapy for up to 13 cycles (approximately 1 year)
- **Arm B**: placebo Q3W + SOC platinum-based doublet chemotherapy Q3W x 4 cycles as neoadjuvant therapy followed by surgery, then post surgery, placebo Q4W up to 13 cycles (approximately 1 year)

Study treatment:

Study Drug for CA20977T		
Medication	**Potency**	**IP/Non-IP**

Nivolumab	100 mg/vial (10 mg/mL)	IP
Carboplatin	450 mg/vial (10 mg/mL)	IP
Cisplatin	100 mg/vial (1 mg/mL)	IP
Docetaxel	80 mg/vial (10 mg/mL)	IP
Paclitaxel Solution	100mg/vial (6 mg/mL)	IP
Pemetrexed Powder	500 mg/vial	IP

Data Monitoring Committee: Yes

References

1 Mountain CA and Dresler CM. Regional lymph node classification for lung cancer staging. Chest. 1997: 1718-23.

2 Goldstraw P, Crowley J, Chansky K, et al for the International Association for the Study of Lung Cancer International Staging Committee. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Onco. 2007; 2(8):706-14.

3 Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest. 2009; 136: 260-71.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA20977T)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Informed Consent Form prior to screening for study participation. Register in the Interactive Response system to obtain participant number. If a participant is re-enrolled, the participant must be re-consented, re-registered in the Interactive Response system to obtain a new participant number and eligibility should be re-confirmed.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization. Participants must be evaluated by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc) during screening.
Medical History	X	All medical history relevant to the disease under study, including the following: any serious organ system dysfunction; prior cancer therapy; Tumor; Node and Metastasis (TNM) stage II, IIIA, and IIIB (T3N2) and smoking history (including electronic cigarettes), documentation of prior COVID-19 vaccine or infection. Within 14 days prior to randomization.
Concomitant Medication Review	X	Within 14 days prior to randomization. Vaccine use within 30 days prior to randomization must be collected.
ECOG Performance Status	X	Within 14 days prior to randomization (Appendix 5)
Safety Assessments		
Physical Examination	X	Includes assessment of symptoms, review of system (ROS), height, weight, BSA (for chemotherapy dosing), and full physical exam within 14 days prior to randomization.
Vital Signs	X	Includes body temperature, respiratory rate, blood pressure, heart rate.
Serious Adverse Events Assessment	X	Serious Adverse Events from the time of consent
Clinical Laboratory Testing	X	All laboratory assessments to be performed within 14 days prior to randomization. Serology must completed within 28 days prior to randomization. See Section 9.4.4 for a list of laboratory tests.

Table 2-1: Screening Procedural Outline (CA20977T)		
Procedure	**Screening Visit**	**Notes**
SARS-CoV-2 Serology	X	Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8])
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) must be performed at screening and within 24 prior to the start of treatment. Serum or urine pregnancy must be performed for at least every 4 weeks on treatment, during pre-surgery period, and during post surgery recovery period. See Appendix 4
Pulmonary Function Test	X	Mandatory PFTs including FVC, FEV1, TLC, FRC, DLco, and oxygen saturation. It is recommended to use same machine and methods throughout study. To be performed within 45 days prior to randomization.
ECG	X	ECG to be performed within 14 days prior to randomization
Imaging Assessments		
Body Imaging	X	PET-CT with contrast is required at screening for all participants and should be acquired up to 45 days prior to randomization. If the CT component of a PET-CT is not of sufficient diagnostic quality for RECIST 1.1 assessment, a separate CT with contrast of the chest, abdomen, pelvis and other suspected areas (in addition to the PET-CT) is required. If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable. See Section 9.1.2 for further details.
Brain Imaging	X	MRI of the brain without and with contrast is required for ALL participants to rule out brain metastases. CT of the brain without and with contrast can be performed if MRI is contraindicated. To be performed within 45 days prior to randomization. See Section 9.1.2 for further details.
Staging mediastinal lymph node evaluation	X	Mandatory mediastinal lymph node evaluation, when clinically feasible. Acceptable method of evaluations include mediastinoscopy, mediastinotomy EBUS, EUS, and CT guided biopsy. An EBUS-TBNA negative for malignancy in a clinically positive mediastinum (PET and or /CT positive mediastinum) should undergo subsequent mediastinoscopy. Note: When enlarged PET positive lymph nodes are visualized at subaortic lymph nodes (station 5) or the para-aortic lymph nodes (station 6), AND if these lymph node stations cannot be biopsied by routine mediastinoscopy due to difficult approach, THEN these participants can enroll without further invasive mediastinal LN evaluation.

Table 2-1: Screening Procedural Outline (CA20977T)		
Procedure	**Screening Visit**	**Notes**
Biomarkers		
EGFR mutation status	X	EGFR mutation status required for all non-squamous participants. Historical results obtained as standard of care prior to screening period are acceptable. Use of a FDA-approved or local Health Authority-approved test (tissue or blood) is strongly encouraged.
Tumor Tissue Sample collection	X	Tumor tissue submission prior to randomization is mandatory. If a recent/archived (within 3 months from randomization) biopsy sample is not available at screening, a fresh biopsy will be taken. Sufficient tumor tissue obtained prior to randomization (FFPE block [preferred] or 5 to 10 unstained slides, obtained from core biopsy, excisional biopsy or surgical specimen). For participants for whom a fresh biopsy is not feasible, archival tumor material obtained within 3 months prior to randomization must be made available. Fine needle aspirate of draining lymph node is not acceptable. Core needle biopsies obtained by EBUS are acceptable. Tumor tissue and pathology report must be submitted to central laboratory and PD-L1 status results available prior to randomization. Tissue requirements are outlined in the CA20977T Laboratory Manual.
Study Treatment		
Randomize	X	PD-L1 will be analyzed by a central laboratory, with results required in IRT prior to randomization Randomize in the Interactive Response system Treatment to be started within 3 calendar days from randomization

Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments (CA20977T)

Procedure	Cycle 1 to 4 Each Cycle Day 1	Pre-surgery (Within 14 Days Before Surgery)	Notes: 1 cycle = 3 weeks
Safety Assessments			
Targeted Physical Examination, Vital Signs, Performance Status	X	X	Targeted physical examination as clinically indicated at each study visit; temperature, heart rate, blood pressure, respiratory rate; and weight. Confirm ECOG performance status (See Appendix 5).
Adverse Events Assessment	Continuously		Collect AEs and SAEs. See Section 9.2. All AEs (SAEs or nonserious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medications	Continuously		Record at each visit during treatment.
Pulmonary Function Test		X	Mandatory PFTs to be re-evaluated prior to surgery only. It is recommended to use same machine and methods throughout study. Includes FVC, FEV1, TLC, FRC, DLco, and oxygen saturation.
ECG		X	To be performed before surgery
Clinical Laboratory Testing	X	X	Hematology and chemistry assessments scheduled for the day of study drug(s) dosing must be available and assessed before dosing. Hematology and chemistry assessments can be drawn within 72 hours prior to dosing. See Section 9.4.4. for a list of laboratory tests
Pregnancy Test (WOCBP only)	See notes		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to Day 1 of each cycle. Serum or urine pregnancy must be performed for at least every 4 weeks on treatment, during pre-surgery period, and during post surgery recovery period. See Appendix 4

Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments (CA20977T)

Procedure	Cycle 1 to 4 Each Cycle Day 1	Pre-surgery (Within 14 Days Before Surgery)	Notes: 1 cycle = 3 weeks
Efficacy Assessments			
Body Imaging		X See notes	A preoperative PET-CT with contrast should be acquired at least 14 days after last neoadjuvant dose and before surgery. If the CT component of a PET-CT is not of sufficient diagnostic quality for RECIST 1.1 assessment, a separate CT with contrast of the chest, abdomen, pelvis and other suspected areas (in addition to the PET-CT) is required. If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable. See Section 9.1.2 for further details.
Brain Imaging		X See notes	Participants should have a brain MRI at least 14 days after last neoadjuvant dose and before surgery, if clinically indicated. CT of the brain without and with contrast prior can be performed prior to surgery if MRI is contraindicated. See Section 9.1.2 for further details.
Pharmacokinetic/Immunogenicity Assessments			
Pharmacokinetics samples	See notes		Refer to Section 9.5
Immunogenicity	See notes		Refer to Section 9.5
Biomarker Assessments			
Biomarker sample collection	See notes	See notes	To be collected before dosing. See Section 9.8.
Collection of optional tumor tissue (if disease progression/recurrence)	See notes		Excised tumor tissue submission (FFPE block [preferred] or 10 to 15 unstained slides) obtained from core biopsy, excisional biopsy, or surgical specimen is optional but strongly encouraged upon disease progression/recurrence and prior to subsequent systemic treatment. Fine needle aspirate of draining lymph node is not acceptable. Core needle biopsies obtained by EBUS are acceptable. See Section 9.8. If a tumor tissue sample is collected, see CA20977T Laboratory Manual for tissue requirements

Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments (CA20977T)

Procedure	Cycle 1 to 4 Each Cycle Day 1	Pre-surgery (Within 14 Days Before Surgery)	Notes: 1 cycle = 3 weeks
Collection of blood sample (if disease progression/recurrence)	See notes		Blood sample collection at the time of disease progression/recurrence is mandatory prior to subsequent systemic treatment. See Section 9.8 and refer to CA20977T Laboratory Manual for sample requirements.
Surgical tumor tissue and lymph node sample collection at time of surgery	See note		Tissue collection from definitive surgical resection is mandatory for • **Central review of pathologic response**: the completed surgical and pathology reports, as well as any photograph or sketches noting the measurements of the primary tumor bed or location of tumor are required. H&E slides from any tumor, tumor bed, and lymph node specimens which were reviewed locally must be submitted for central pathology review. Additionally, all H&E slides (1 stained slide per block) from all of the blocks from surgery are submitted for central pathology review. • **Biomarker assessments:** Submission of the following is required: 1 tumor block (Preferred, consisting of 2-3 pieces 3-5 mm in size) or 15 unstained slides obtained from a similar surgical specimen. Tissue requirements are outlined in CA20977T Laboratory Manual.
Outcomes Assessments			
NSCLC-SAQ	X	X	Completed prior to treatment at each cycle and pre-surgery visit. See Section 9.1.4 for further details.
PGIS	X	X	Completed prior to treatment at each cycle and pre-surgery visit. See Section 9.1.4 for further details.
PROMIS PF 8c	X	X	Completed prior to treatment at each cycle and pre-surgery visit. See Section 9.1.4 for further details.
FACT-L	X	X	Completed prior to treatment at each cycle and pre-surgery visit. See Section 9.1.4 for further details.
EQ-5D-3L	X	X	Completed prior to treatment at each cycle and pre-surgery visit. See Section 9.1.4 for further details.

Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments (CA20977T)

Procedure	Cycle 1 to 4 Each Cycle Day 1	Pre-surgery (Within 14 Days Before Surgery)	Notes: 1 cycle = 3 weeks
HCRU (Health Care Resource Utilization)	X	X	Health care resource utilization data will be collected at each visit by study site staff using the case report form (CRF)
Study Treatment			
IRT Drug Vial Assignments	X		Register the visit in the Interactive Response system for drug allocation (performed by unblinded site staff)
Dispense Study treatment	X		See Section 7 for complete details.

Table 2-3:	**Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments (CA20977T)**		
Procedure	**Post surgery/Pre-adjuvant Visit[a] (after post surgery recovery period of 30-90 days)**	**Cycle 1 to Cycle 13[b] Each Cycle Day 1 1 cycle = 4 weeks 1 year of treatment**	**Notes**
Safety Assessments			
Adverse Event and Serious Adverse Event Assessments	Continuously		All AEs (SAEs or nonserious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. See Section 9.2.
Concomitant Medication Review	Continuously		Record at each visit during treatment.
Targeted Physical Examination	X	X	Vital Signs: temperature, heart rate, blood pressure, and respiratory rate; and weight. Confirm ECOG performance status (Appendix 5)
Laboratory Tests			
Clinical Laboratory Testing	X	X	Hematology and chemistry assessments scheduled for the day of study drug(s) dosing must be available and assessed before dosing. Hematology and chemistry assessments can be drawn within 72 hours prior to dosing. See Section 9.4.4. for a list of laboratory tests to conduct
Pregnancy Test (WOCBP only)	See notes		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to Day 1 of each cycle. Serum or urine pregnancy must be performed for at least every 4 weeks on treatment, during pre-surgery period, and during post surgery recovery period. See Appendix 4
Biomarker Assessments			
Biomarker Sample Collection	See notes	See notes	See section 9.8
Collection of optional tumor tissue (if disease progression/recurrence)	See note		At time of disease progression or recurrence (see Section 9.8) Excised tumor tissue submission (FFPE block [preferred] or 10 to 15 unstained slides), obtained from core biopsy, excisional biopsy, or surgical specimen is

Table 2-3:	Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments (CA20977T)		
Procedure	**Post surgery/Pre-adjuvant Visit[a] (after post surgery recovery period of 30-90 days)**	**Cycle 1 to Cycle 13[b] Each Cycle Day 1 1 cycle = 4 weeks 1 year of treatment**	**Notes**
			optional but strongly encouraged upon disease progression/recurrence and prior to subsequent systemic treatment. Fine needle aspirates of draining lymph node are not acceptable. Core needle biopsies obtained by EBUS are acceptable. If a sample is collected, see CA20977T Laboratory Manual for tissue requirements.
Collection of blood sample (if disease progression/recurrence)	See note		Blood sample collection at the time of disease progression is mandatory prior to subsequent systemic treatment. See section 9.8 and refer to CA20977T Laboratory Manual for sample requirements.
Efficacy Assessments			
Body Imaging	X	See notes	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease. If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable. The first tumor assessment post surgery should occur within 1 week prior to initiation of study adjuvant treatment. Subsequent assessment should occur every 12 weeks (± 7 days) for up to and including 108 weeks (approximately 2 years) following first dose of adjuvant treatment, then every 24 weeks (±14 days) for up to and including Week 276 (approximately 5 years) or until disease recurrence or disease progression is confirmed by blinded independent central review (BICR) and, in addition, continue until investigator-assessed distant metastasis. Participants that do not undergo surgery will continue to have tumor assessments every 12 weeks (±7 days) for up to and including 108 weeks (approximately 2 years), (following the pre-surgery PET-CT scan) then every 24 weeks (±14 days) for up to and including Week 276 (approximately 5 years) or until disease

Table 2-3: Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments (CA20977T)			
Procedure	**Post surgery/Pre-adjuvant Visit[a] (after post surgery recovery period of 30-90 days)**	**Cycle 1 to Cycle 13[b] Each Cycle Day 1 1 cycle = 4 weeks 1 year of treatment**	**Notes**
			recurrence or disease progression is confirmed by BICR and, in addition, continue until investigator-assessed distant metastasis. See Section 9.1.2 for further details.
Body Brain Imaging	X	See notes	Participants should have a brain MRI, if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.2 for further details.
Pharmacokinetic/Immunogenicity Assessments			
Pharmacokinetics		See notes	See 9.5 for further details.
Immunogenicity		See notes	See 9.5 for further details.
Outcomes Assessments			
NSCLC-SAQ	X	X	Completed at post surgery visit and prior to treatment at each cycle. See Section 9.1.4 for further details.
PGIS	X	X	Completed at post surgery visit and prior to treatment at each cycle. See Section 9.1.4 for further details.
PROMIS PF 8c	X	X	Completed at post surgery visit and prior to treatment at each cycle. See Section 9.1.4 for further details.
FACT-L	X	X	Completed at post surgery visit and prior to treatment at each cycle. See Section 9.1.4 for further details.
EQ-5D-3L	X	X	Completed at post surgery visit and prior to treatment at each cycle. See Section 9.1.4 for further details.

Table 2-3:	**Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments (CA20977T)**		
Procedure	**Post surgery/Pre-adjuvant Visit[a] (after post surgery recovery period of 30-90 days)**	**Cycle 1 to Cycle 13[b] Each Cycle Day 1 1 cycle = 4 weeks 1 year of treatment**	**Notes**
Healthcare Resource Utilization	X	X	Healthcare resource utilization data will be collected at each visit by study site staff using the case report form (CRF).
Administer Study Drug			
IRT Drug Vial Assignments		X	Register the visit in the Interactive Response system for drug allocation (performed by unblinded site staff) Register the study drug discontinuation at the end of the study treatment period in the Interactive Response system
Dispense Study treatment		X	See Section 7 for complete details. Participants should be treated within 90 days from surgery.

[a] Participants who have not had definitive surgical resection, may continue onto adjuvant cycles 1-13 and follow the post surgery on study assessments (See Section 5.1.2.3)

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

Note: Some assessments referred to in this section may not be captured as data in the CRF. These assessments are intended to be used as safety monitoring by the investigator. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations

Table 2-4: Long-term Follow-up Assessments (CA20977T)				
Procedure	**Follow-up Visit 1[a,b]**	**Follow-up Visit 2[a,b]**	**Disease Surveillance and Survival Follow-up[c]**	**Notes**
Survival status	X	X	X	Survival status should be obtained every 3 months (± 14 days) after Follow-up Visit 2.
Subsequent anti-cancer therapy	X	X	X	The date of disease progression and response to anti-cancer subsequent therapy will be collected.
Safety Assessments				
Targeted Physical Examination	X	X		Vital Signs: blood pressure, heart rate, temperature, respiratory rate; and weight. ECOG performance status (Appendix 5)
Serious Adverse Events Assessment	X	X		All SAEs must be collected within 100 days of the last dose of study treatment and followed until SAE is resolved. Participants will be followed for all SAEs, nonserious AEs of special interest (as defined in Section 9.2.1), and all AEs (SAEs and nonserious 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.
Adverse Events Assessment	X	X		All AEs must be collected within 100 days of the last dose of study treatment
Concomitant Medications	X	X		
Subsequent anti-cancer therapy	X	X	X	
Laboratory Tests				
Clinical Laboratory Testing	X	X	See note	See Section 9.4.4 for a list of laboratory tests to conduct Collect hematology and chemistry at FU1 and FU2 and until all previous toxicities have resolved. See Section 9.2.6.

Table 2-4: Long-term Follow-up Assessments (CA20977T)				
Procedure	**Follow-up Visit 1[a,b]**	**Follow-up Visit 2[a,b]**	**Disease Surveillance and Survival Follow-up[c]**	**Notes**
Pregnancy Test (WOCBP)	See notes			Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done every 4 weeks for 6 months or longer as per the local regulation and approved product label (for nivolumab and chemotherapy regimens specified as study treatment in the protocol) after the last dose of study treatment. See Appendix 4 Serum or urine pregnancy test must be performed prior to imaging
Efficacy Assessment,				
Body imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease. (Section 9.1.2 for further details). If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable. **For participants that undergo definitive surgery,** the first tumor assessment should occur within 1 week prior to adjuvant treatment and will follow the outlined schedule for ongoing tumor assessments. Imaging should be continued for a maximum of 5 years from the first dose of adjuvant treatment or until BICR confirmed disease progression or recurrence and, in addition, continue until investigator-assessed distant metastasis at intervals of: • Every 12 weeks (± 7 days) during Year 1 and Year 2 (for up to and including 108 weeks from first dose of adjuvant treatment) • Every 24 weeks (± 14 days) during Year 3, Year 4 and Year 5 (for up to and including 276 weeks) **For participants that do not undergo surgery** should align with ongoing tumor assessments. Imaging should be continued for a maximum of 5 years from the pre-surgery PET-CT scan or until BICR confirmed disease progression or recurrence and, in addition, continue until investigator-assessed distant metastasis at intervals of: • Every 12 weeks (± 7 days) during Year 1 and Year 2 (for up to and including 108 weeks from presurgery PET scan) • Every 24 weeks (± 14 days) during Year 3, Year 4 and Year 5 (for up to and including 276 weeks from presurgery PET scan) See Section 9.1.2 for further details.			

Table 2-4: Long-term Follow-up Assessments (CA20977T)				
Procedure	**Follow-up Visit 1[a,b]**	**Follow-up Visit 2[a,b]**	**Disease Surveillance and Survival Follow-up[c]**	**Notes**
Brain Imaging	Only for participants without BICR-confirmed progression or recurrence and without investigator-assessed progression precluding surgery. Participants should have a brain MRI, if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.2 for further details.			
Biomarkers				
Biomarker sample collection	See notes			See Section 9.8.
Collection of optional tumor tissue upon disease progression/recurrence	See notes			At time of disease progression or recurrence (see Section 9.8) Excised tumor tissue submission (FFPE block [preferred] or 10 to 15 unstained slides), obtained from core biopsy, excisional biopsy, or surgical specimen is optional but strongly encouraged upon disease progression/recurrence and prior to subsequent systemic treatment. Fine needle aspirates of draining lymph node are not acceptable. Core needle biopsies obtained by EBUS are acceptable. If a sample is collected, see CA20977T Laboratory Manual for tissue requirements If disease is inaccessible at disease progression/recurrence, tumor tissue can be accessed later in the disease course (if available) with intervening therapy documented in the CRF.
Collection of blood sample upon disease progression/recurrence	See notes			Blood sample collection at the time of disease progression is mandatory prior to subsequent systemic treatment. See section 9.8 and refer to CA20977T Laboratory Manual for sample requirements.
Outcomes Assessments				
NSCLC-SAQ	X	X	X	To be administered during the Follow-up Visits 1 & 2 and at each study visit during disease surveillance. See Section 9.1.4 for
PGIS	X	X	X	

Table 2-4: Long-term Follow-up Assessments (CA20977T)				
Procedure	**Follow-up Visit 1[a,b]**	**Follow-up Visit 2[a,b]**	**Disease Surveillance and Survival Follow-up[c]**	**Notes**
PROMIS PF 8c	X	X	X	further details. Survival visits may be conducted in person or by telephone (if by telephone, only EQ-5D-3L (phone) outcome assessments questionnaire should be collected).
FACT-L	X	X	X	
EQ-5D-3L	X	X	X	
Healthcare Resource Utilization	X	X	X	Healthcare resource utilization data will be collected at each visit by study site staff using the case report form (CRF).

[a] Participants must be followed for at least 100 days after the last dose of study treatment. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. 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. For participant who did not undergo adjuvant treatment after surgery, FU1 should occur 30 days from post-surgery visit (± 7 days). FU2 should occur approximately 100 days (± 7 days) from post-surgery visit. 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 CRF. These assessments are intended to be used as safety monitor by the investigator. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[c] Survival follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit 2. Survival visits may be conducted in person or by telephone. Bristol-Myers Squibb may request that survival data be collected on all treated participants outside of the 3-month specified window.

3 INTRODUCTION

CA20977T is a phase 3, randomized, double-blinded Study of neoadjuvant chemotherapy plus nivolumab versus neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage IIA-IIIB non-small cell lung cancer.

Approximately 80% of lung cancer cases are NSCLC, with most patients presenting with late stage disease. Of patients with NSCLC, 20% present with stage I or II disease, whereas 30% present with stage III disease and 50% with stage IV disease. Patients with pathologic stage I NSCLC have a 5-year survival of approximately 60%. Stage II to III NSCLC patients have a 5-year survival of approximately 25% to 40%.[1] Therefore, earlier diagnosis and treatment of NSCLC at stage II will provide better micrometastatic disease control, which may support greater survival.

CA20977T is a phase 3, randomized, double-blinded study of neoadjuvant chemotherapy plus nivolumab versus neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage IIA-IIIB non-small cell lung cancer. The study will allow for direct comparison of nivolumab plus chemotherapy versus SOC chemotherapy alone in the periadjuvant setting. The study is designed with an analysis of event free survival (EFS) as the primary end point and pathologic complete response (pCR) rate as the key secondary endpoint.

3.1 Study Rationale

The early-stage (IIA-IIIB) NSCLC represents a population of high unmet need with a 5-year survival rate of 25-50%. A rational approach to improve survival in these patients is to eradicate micrometastatic disease and to minimize the risk of relapse with neoadjuvant and adjuvant maintenance therapy.

The SOC treatment comprises adjuvant or neoadjuvant platinum-based doublet chemotherapy for patients with operable stage IB-IIIA NSCLC or chemoradiation for patients with unresectable stage IIIA/B NSCLC. Preoperative or neoadjuvant chemotherapy has been assessed in a number of trials for patients with operable NSCLC. A meta-analysis based on 7 trials involving 988 patients suggested that neoadjuvant chemotherapy improved OS when given preoperatively in a similar magnitude to those observed with adjuvant chemotherapy. Neoadjuvant immunotherapy in combination with chemotherapy offers the possibility achieving enhanced pathological complete response rate compared to SOC chemotherapy alone. In addition, it also allows for the identification of surrogate clinical and biological markers that may correlate with response to therapy and a potential long-term outcome. Randomized trials are currently ongoing to explore the potential benefit of nivolumab in the neoadjuvant, adjuvant, and locally advanced unresectable NSCLC setting. In addition, the safety and efficacy profile of neoadjuvant nivolumab monotherapy or combination therapy (nivolumab plus chemotherapy) are being evaluated in ongoing trials.

Emerging phase 1/2 data provides the early encouraging signal of nivolumab or nivolumab in combination with chemotherapy as neoadjuvant therapy with increasing major pathological

response rate and pathological complete response rates, respectively, with no delay in surgery and tolerable safety profile. Data from NADIM trial (NCT03081689), a phase 1/2 study evaluating nivolumab given concomitantly with chemotherapy indicated this combination, was well tolerated thus far with no major increase in prohibitive toxicity, including pneumonitis. Data from this phase 2 study presented at the 19th World Conference on Lung Cancer showed 18 patients (75.0%) achieved complete response, while 24 patients (80.0%) had a major pathologic response. Overall, periadjuvant scheduling with combination of immunotherapy and chemotherapy in the neoadjuvant setting followed by immunotherapy maintenance in the adjuvant setting following definitive surgery may offer enhanced efficacy with improved survival with an acceptable toxicity profile.

This study of nivolumab and chemotherapy followed by continued adjuvant nivolumab after surgical resection, aims to demonstrate that treatment with nivolumab combined with chemotherapy in neoadjuvant phase and maintenance with nivolumab in the adjuvant phase will significantly prolong EFS and increase the rate of pCR in participants with resectable Stage IIA-IIIB non-small cell lung cancer.

3.1.1 Research Hypothesis

The incorporation of nivolumab to neoadjuvant chemotherapy with adjuvant maintenance will prolong event-free survival (EFS) and increase overall survival (OS), as compared with neoadjuvant chemotherapy as SOC in participants with newly diagnosed, resectable NSCLC.

3.2 Background

Surgical resection remains the mainstay of treatment for stage I and II patients; however, despite potential curative surgery, approximately 27% of stage IB and 35-59% of stage II-IIA NSCLC patients will relapse and eventually die of their disease.[2] With enhanced lung cancer screening techniques, the percentage of those diagnosed during the early stages may increase over the duration of the trial. The eighth edition of the TNM staging system is used to determine the staging for NSCLC.[3] Patients with pathologic stage IA1 NSCLC have a 5-year survival of approximately 90%. Stage II to III NSCLC patients have a 5-year survival of approximately 12% to 65%.[4]

A rational approach to improve survival in these patients is to eradicate micrometastatic disease and to minimize the risk of relapse with adjuvant or neoadjuvant chemotherapy. Many adjuvant studies have been performed, and these trials are summarized in Table 3.2-1. Although there are some conflicting results, the overall evidence from these studies suggests that adjuvant platinum-based doublet chemotherapy is beneficial for good Performance Status patients with stage ≥ II disease. The benefit to stage IB patients is less clear and may depend on the size of the primary tumor (eg, Stage Ib) and other risk factors. A 2010 meta-analysis including both older and more recent trials confirmed the survival benefit shown in the LACE meta-analysis and also suggested a benefit of adjuvant chemotherapy for stage IB disease.[5]

Table 3.2-1: Select Adjuvant NSCLC Studies						
Trial	**Stage**	**Treatment**	**# of Pts**	**5 Yr OS**	**HR**	**P Value**
ECOG 1505	I-III	Cis-doublet Cis-double+Bev	749 752	72 mo mOS in both arms	0.99	0.9
ALPI	I – III	Surg MVP	603 601	45% 50%	0.96	0.59
IALT	I – III	Surg Cis-based	935 932	40% 44.5%	0.86	<0.03
ANITA	IB - IIIA	Surg Cis-Vin	433 407	43% 51%	0.80	0.017
BLT	I – IIIA	Surg Cis-based	189 192	58% 60%	1.02	0.90
NCIC/JBR10	IB – II	Surg Cis-Vin	240 242	54% 69%	0.69	0.03
CALGB	IB	Surg Carb-pac	171 173	57% 59%	0.80	0.10
ALPI	I – III	Surg MVP	603 601	45% 50%	0.96	0.59

ALPI, Adjuvant Lung Cancer Project Italy; OS, overall survival; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group, IALT, International Adjuvant Lung Cancer Trial; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; NCI-C, National Cancer Institute-Canada; CALGB, Cancer and Leukemia Group B; MVP, mitomycin, vindesine, cisplatin; Cis-Vin, cisplatin-vinorelbine; Carb-pac, carboplatin-paclitaxel.

The early-stage (IB-III) NSCLC represents a population of high unmet need with a 5-year survival rate of 25-50%.[6] The current available standard of care (SOC) only provides a 5% absolute improvement in 5-year overall survival (OS).[2,7,8,9] The SOC comprises adjuvant or neoadjuvant platinum-based doublet chemotherapy for patients with operable stage IB-IIIA NSCLC or chemoradiation for patients with unresectable stage IIIA/B NSCLC. Follow-up of adjuvant trials are long and may require decades before a new treatment is introduced into clinical practice. Preoperative or neoadjuvant chemotherapy has been assessed in a number of trials for patients with operable NSCLC. A meta-analysis based on 7 trials involving 988 patients suggested that neoadjuvant chemotherapy improved OS when given preoperatively in a similar magnitude to those observed with adjuvant chemotherapy.[10]

Randomized trials are currently on-going to explore the potential benefit of nivolumab in the neoadjuvant, adjuvant, and locally advanced unresectable NSCLC setting. In addition, the safety and efficacy profile of neoadjuvant nivolumab monotherapy or combination therapy (nivolumab plus chemotherapy) are being evaluated in ongoing trials.

Emerging phase 1/2 data provides the early encouraging signal of nivolumab or nivolumab in combination with chemotherapy as neoadjuvant therapy with increasing MPR or pCR rates,

respectively, with no delay in surgery and tolerable safety profile. Preliminary data from NADIM trial (NCT03081689) which is a phase 1/2 study to evaluate nivolumab given concomitantly with chemotherapy indicated this combination, was well tolerated thus far with no major increase in prohibitive toxicity, including pneumonitis.[11] Overall, periadjuvant scheduling of immunotherapy with chemotherapy may offer enhanced efficacy with an acceptable toxicity profile.

This periadjuvant phase 3 study (CA20977T) will evaluate the clinical efficacy and will establish the safety of neoadjuvant therapy of nivolumab plus platinum-based doublet chemotherapy followed by adjuvant therapy of nivolumab in resectable lung cancer. Specifically, this study will compare EFS and OS and estimate pCR rate among participants treated with periadjuvant therapy.

3.2.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[12,13,14] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[15] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[16] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[17] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus

isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[18]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the Nivolumab Investigators Brochure.

3.2.2 Clinical Activity of Immuno-oncology Treatment Combined with Chemotherapy

The combination of immuno-oncology agents and traditional chemotherapy has been explored. In addition to the additive effects of combining drugs with different mechanisms of action, emerging evidence indicates that one of the mechanisms of actions of chemotherapy is via activation of the immune system through multiple pathways.[8] The subsequent cytotoxic cell death from chemotherapies and subsequent antigen release may provide immune stimulation. Certain chemotherapy regimens have a broad effect on cell death and physiological response. As an example, cyclophosphamide reduces the number of circulating Treg cells, which are a key component in immunosuppression and gemcitabine has also been shown to reduce MDSCs and hence interferon-gamma, which have inhibitory roles in the immune response.[19, 20] The dual role of cytotoxicity and immune activation from chemotherapy has provided the biological rationale for the development of combinations with immunotherapy.[21]

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive patients with advanced NSCLC in study Checkmate 012. Nivolumab 10 mg/kg was combined with gemcitabine and cisplatin or pemetrexed + cisplatin. Nivolumab 10 mg/kg and 5 mg/kg were combined with paclitaxel and carboplatin.

The safety profile of nivolumab plus platinum-based doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines. No dose-limiting toxicities were observed during first 6 weeks of treatment. The frequency of most immune-related select AEs was higher for the combination than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths. Pneumonitis of any grade was reported in 7 participants (13%): Grade 3-4 in 4 participants (7%). Twelve (21%) participants discontinued due to treatment-related AEs.

Table 3.2.2-1: Safety in CA209012

	Total (N=56)		
	All Grades	**Grade 3**	**Grade 4**
Participants with any treatment-related AE, % (n)	95 (53)	41 (23)	4 (2)[a]
Treatment-related AE in >15% of Patients, % (n)			
Fatigue	71(40)	5 (3)	0
Nausea	46 (26)	2 (1)	0

Table 3.2.2-1: Safety in CA209012			
	Total (N=56)		
	All Grades	Grade 3	Grade 4
Decrease Appetite	36 (20)	2 (1)	0
Alopecia	30 (17)	0	0
Anemia	27 (15)	4 (2)	0
Rash	27 (15)	2 (1)	0
Arthralgia	21 (12)	0	0
Diarrhea	21 (12)	2 (1)	0
Constipation	20 (11)	0	0
Peripheral Neuropathy	20 (11)	0	0

[a] Grade 4 events: neutrophil count decreased (n = 1), pneumonitis and neutropenia (n = 1 each; occurred in the same patient).

The overall response rate across all the nivolumab and chemotherapy cohorts ranged from 33-47% and median duration of response was 27.3 weeks (see Table 3.2.2-2). Activity was evaluated by PD-L1 expression and was observed in participants with both PD-L1 expressing and non-expressing tumors. Overall, 79% (44/56) of participants had evaluable tumor samples. At the ≥ 1% expression level, the response rate was 48% and 43% for expressers and non-expressers, respectively. The 1-year OS was 70% and 76% for expressers and non-expressers, respectively.

Table 3.2.2-2: Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012				
	Nivolumab 10 mg/kg			Nivolumab 5 mg/kg
	Gem/Cis (n=12)	Pem/Cis (n=15)	Pac/Carb (n=15)	Pac/Carb (n=14)
ORR, %	33	47	47	43
SD, %	58	47	27	43
Median Duration of Response, Weeks	45	24.4	2.3	27.3
12-mo OS rate, %	50	87	7	86
18-mo OS Rate, %	33	60	40	62
Median OS, Weeks	51	83	65	Not Reached

In the ongoing CheckMate 227 trial, in the setting of first line NSCLC with <1% tumor PD-L1 expression, PFS was improved with nivolumab plus chemotherapy vs chemotherapy (mPFS: 5.6m vs 4.7m; HR=0.74 [95% CI: 0.58 to 0.94]), ORR was 36.7% in nivolumab plus chemotherapy arm, 23.1% in chemotherapy arm, mDOR was 7.2 months in nivolumab plus chemotherapy arm, 4.7 months in chemotherapy arm. The rate of grade 3 or 4 treatment-related adverse events was

52% with nivolumab plus chemotherapy, 35% with chemotherapy, Overall, the safety profile and efficacy are consistent with previously reported data for nivolumab plus chemotherapy, as well as data from other PD-(L)1 blockades in combination with chemotherapy.

The early clinical data is emerging to show the benefit of immunotherapy and chemotherapy combination in early NSCLC setting. The nivolumab in combination with paclitaxel and carboplatin has shown increased pathological response rate in IIIA NSCLC patients. Similarly, combination of atezolizumab in combination with carboplatin and nab-paclitaxel has demonstrated significant activity in neoadjuvant setting. In both trials, combination of immunotherapy with chemotherapy has been well tolerated in patients with early stage NSCLC.

The clinical activity of nivolumab observed to date in NSCLC, including 2 positive phase 3 studies demonstrated prolonged survival with nivolumab monotherapy compared to docetaxel in squamous and non-squamous NSCLC after platinum failure. CA209057 (An Open-Label Randomized Phase III Trial of Nivolumab versus Docetaxel in Previously Treated Metastatic NSCLC) study demonstrated OS was superior for participants receiving nivolumab compared to those receiving docetaxel. Higher confirmed ORRs in PDL1 expressers were seen in the combination arm compare to the nivolumab monotherapy arm in CA209012 (A Multi-arm Phase I Safety Study of Nivolumab in Combination with Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects with Stage IIIB/IV NSCLC).

3.3 Benefit/Risk Assessment

Extensive details on the safety profile of nivolumab or in combination with chemotherapy are available in the Investigator Brochure, and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy 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 have been developed; these are provided in Appendix 06. 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.

The early-stage (IIA-IIIB) NSCLC represents a population of high unmet need with a 5 year survival rate of 25-50%. The current available SOC, including adjuvant or neoadjuvant platinum-based doublet chemotherapy, only provides a 5% absolute improvement in 5-year OS. Combining nivolumab with SOC has the potential for increased clinical benefit compared to SOC alone.

Data is emerging to show the clinical benefit of nivolumab and chemotherapy combination in early NSCLC. Preliminary data from ongoing phase 2 trial of neoadjuvant nivolumab plus platinum-based doublet chemotherapy showed striking pCR rate. Preliminary experience gained from these

ongoing phase 2 trials with neoadjuvant nivolumab and nivolumab-based combinations suggests these study treatments were well tolerated. The platinum-based doublet chemotherapy regimens have well described safety profiles, characterized by myelosuppression and other regimen-specific non-hematologic toxicities, such as peripheral neuropathy, nausea/vomiting, and renal impairment.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the event-free survival (EFS) by blinded independent central review (BICR) in Arm A vs Arm B participants	EFS is defined as the length of time from randomization to any of the following events: progression of disease or worsening of disease precluding surgery, if surgery is attempted but gross resection is abandoned due to unresectable tumor or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause. Progression/recurrence will be assessed by BICR per RECIST 1.1. Participants who do not undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 progression or death.
Secondary	
To compare the overall survival (OS) in Arm A vs Arm B participants	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 subject was known to be alive.
To assess the pathologic complete response (pCR) rate by BIPR in Arm A vs Arm B participants	pCR rate is defined as the number of randomized participants with absence of residual viable tumor in lung and lymph nodes as evaluated by blinded independent pathology review (BIPR), divided by the number of randomized participants for each treatment group.
To assess the major pathological response (MPR) rate by BIPR in Arm A vs Arm B participants	MPR rate is defined as number of randomized participants with ≤10% residual viable tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group.
To assess safety and tolerability in Arm A vs Arm B participants	Incidence of AEs, SAEs, and select AEs

Table 4-1: Objectives and Endpoints	
Objectives	**Endpoints**
Exploratory	
To assess objective response rate (ORR) by BICR in Arm A vs Arm B participants	ORR is defined as proportion of all randomized participants whose overall radiological response prior to definitive surgery (no confirmation required) is either a complete response or partial response per RECIST 1.1 criteria by BICR. For participants without surgery, the first scheduled tumor assessment per protocol will be used to assess ORR. Participants who received alternative anticancer therapy before the presurgery tumor assessment will be counted as nonresponders.
To assess time to death or distant metastasis (TTDM) as reported by investigator in Arm A vs Arm B participants	TTDM is defined as the time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the thorax or in the contralateral lung using RECIST 1.1 as reported by investigator. Participants who have not developed distant metastasis or died at the time of analysis will be censored on the date of their last evaluable tumor assessment.
To assess the event-free survival (EFS) by blinded independent central review (BICR), overall survival (OS), MPR rate, and pCR rate in Arm A vs Arm B participants by PD-L1 status	EFS, OS, MPR rate, and pCR rate as previously defined
To assess the feasibility of surgery and rate of peri- and post operative complications (within 90 days of surgery) in Arm A vs Arm B participants	Proportion of delayed or canceled surgery, duration of surgery, length of hospital stay, surgical approach, incidence of AE/SAE associated with surgery including intraoperative complications (eg, pneumonitis, ARDS, PRBC, bronchopleural fistulas, airleaks, etc), re-admission to the Intensive Care Unit, atrial fibrillation. other supraventricular tachycardia (SVT), etc to 90 days post surgery
To assess changes in disease-related symptoms and impacts on health-related quality of life in Arm A vs Arm B participants	Time to symptom deterioration, proportion of participants without meaningful symptom deterioration, based on the NSCLC-SAQ and the LCS subscale of the FACT-L. Mean change from baseline in FACT-L total and subscale scores and NSCLC-SAQ total score
To assess changes in health status and health-related quality of life.	Mean change from baseline, time to deterioration, proportion of participants without meaningful deterioration in EQ-5D-3L VAS and Utility Index
To assess changes in physical function	Mean change from baseline in PROMIS T-score based on the PROMIS PF 8c

Table 4-1: Objectives and Endpoints	
Objectives	**Endpoints**
To characterize participant perceptions of the bothersomeness of symptomatic AEs.	GP5 item from the FACT-L
Assess the measurement properties of the NSCLC-SAQ.	Reliability, validity and responsiveness of the NSCLC-SAQ
To characterize the immunogenic potential of nivolumab	Anti-nivolumab antibodies and their relationship with other outcome measures
To characterize PK of nivolumab	PK measurements of nivolumab
To evaluate the efficacy after next line of treatment	PFS after next line of treatment (PFS2)
To evaluate candidate predictive biomarkers including, but not limited to, biomarkers within the tumor (e.g. tumor inflammatory gene expression signatures, driver mutations, immune cell infiltrates, etc) as well as within the periphery (eg, ctDNA, soluble inflammatory / immunosuppressive factors, as potential predictive biomarkers of efficacy)	Gene expression signatures (eg. tumor inflammation, immune cell infiltration etc), driver mutations (e.g. STK11, KRAS) as well as peripheral markers and soluble factors within blood (eg, cytokines, solHLA) and other factors within blood (eg, MDSC) and their association with clinical outcomes (EFS, pCR, mMPR, OS, cRR) Circulating tumor DNA for blood TMB and/or MRD analysis.

5 STUDY DESIGN

5.1 Overall Design

This is a randomized, double blind, multicenter phase 3 study for participants with early stage (Stage IIA [> 4 cm] to IIIB [T3N2 only]) NSCLC evaluating Arm A with the comparator arm (Arm B). This study will examine if periadjuvant (neoadjuvant, then adjuvant) immunotherapy will prolong event free survival in participants with early stage (Stage IIA [> 4 cm] to IIIB [T3N2 only]) NSCLC.

Participants will be randomized (1:1 ratio) across 2 treatment arms:

- **Arm A**: nivolumab 360 mg Q3W + SOC platinum-based doublet chemotherapy Q3W x 4 cycles as neoadjuvant treatment followed by surgery; then post surgery nivolumab 480 mg Q4W adjuvant treatment for up to 13 cycles (approximately 1 year)
- **Arm B**: placebo Q3W + SOC platinum-based doublet chemotherapy Q3W x 4 cycles as neoadjuvant treatment followed by surgery, then post surgery placebo Q4W for up to 13 cycles (approximately 1 year)

The study is divided into screening period, neoadjuvant / pre-surgery treatment period, surgical period, adjuvant / post surgery treatment period, and disease surveillance/long-term follow-up period.

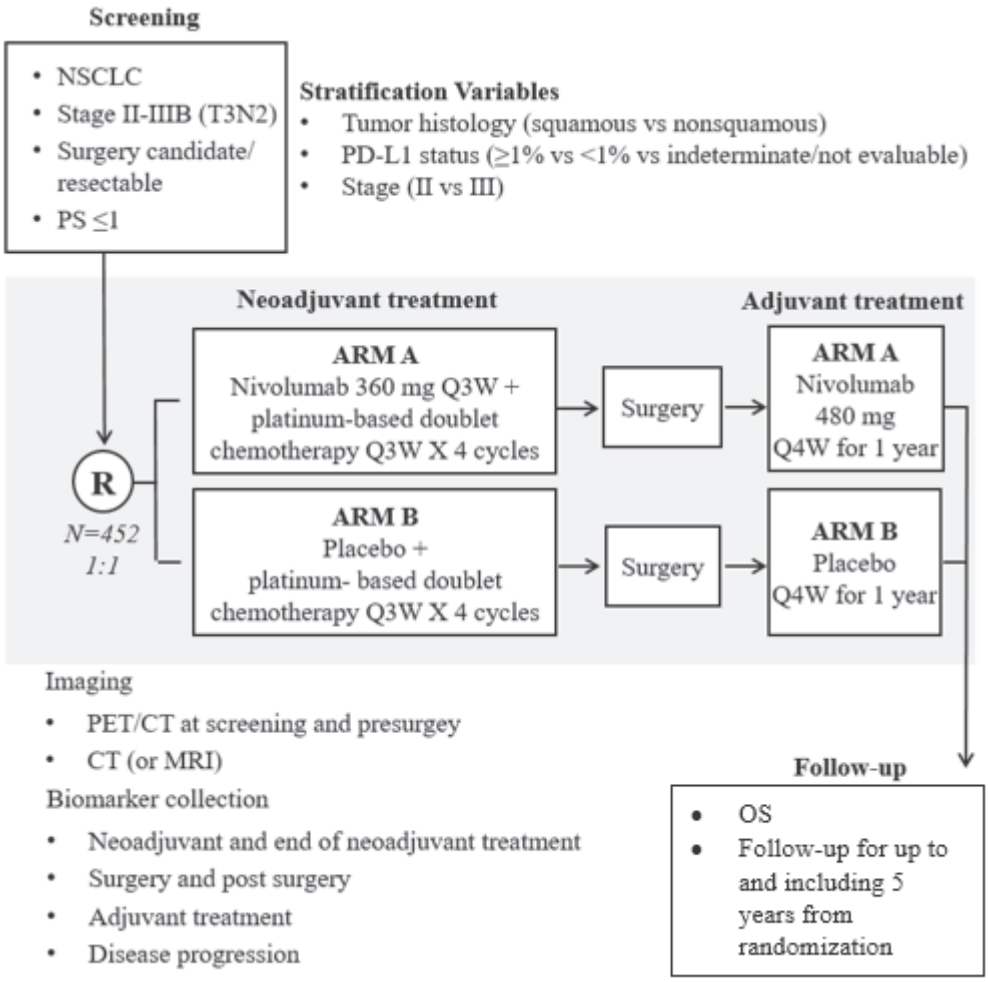
Randomization will be stratified by the following:

- Tumor histology (squamous/non-squamous)
- NSCLC Stage (II vs III)
- PD-L1 status
  - ≥1%
  - <1%
  - indeterminate or not evaluable
- PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample and categorized as follows:
  - PD-L1 positive is defined as ≥1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
  - PD-L1 negative is defined as <1% tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
  - PD-L1 indeterminate is defined as participants with indeterminate (<1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells/tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content) insufficient sample quantity or quality to stain for PD-L1 status or those participants in whose samples PD-L1 status could not be determined despite appropriate amounts of tissue sample. No more than 10% of participants randomized in this trial will be PD-L1 indeterminate and not evaluable category.

Total duration of the study from start of randomization to final analysis of EFS is expected to be approximately 38 months, assuming 23 months accrual duration. Final analysis of OS is expected to be 46 months after the start of randomization.

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

Figure 5.1-1: CA20977T Schema



5.1.1 Screening

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. After signing the informed consent form (ICF), participants will be evaluated for entry criteria during the Screening period before randomization. The screening assessments are shown in Table 2-1.

Participants must be evaluated by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc) to confirm eligibility during screening. The multidisciplinary team review must be documented in medical record and CRF. Tumor tissue submission prior to randomization is mandatory. If a recent/archived (within 3 months from randomization) biopsy sample is not available at screening, a fresh biopsy will be taken.

Sufficient tumor tissue obtained prior to randomization (FFPE block or 5 to 10 unstained slides, obtained from core biopsy, excisional biopsy or surgical specimen) is acceptable.

For participants for whom a fresh biopsy is not feasible, archival tumor material obtained within 3 months prior to randomization must be made available. Fine needle aspirate of draining lymph node is not acceptable. Core needle biopsies obtained by EBUS are acceptable.

Tumor tissue and pathology report must be submitted to central laboratory and PD-L1 status results available prior to randomization. Tissue requirements are outlined in CA20977T Laboratory Manual.

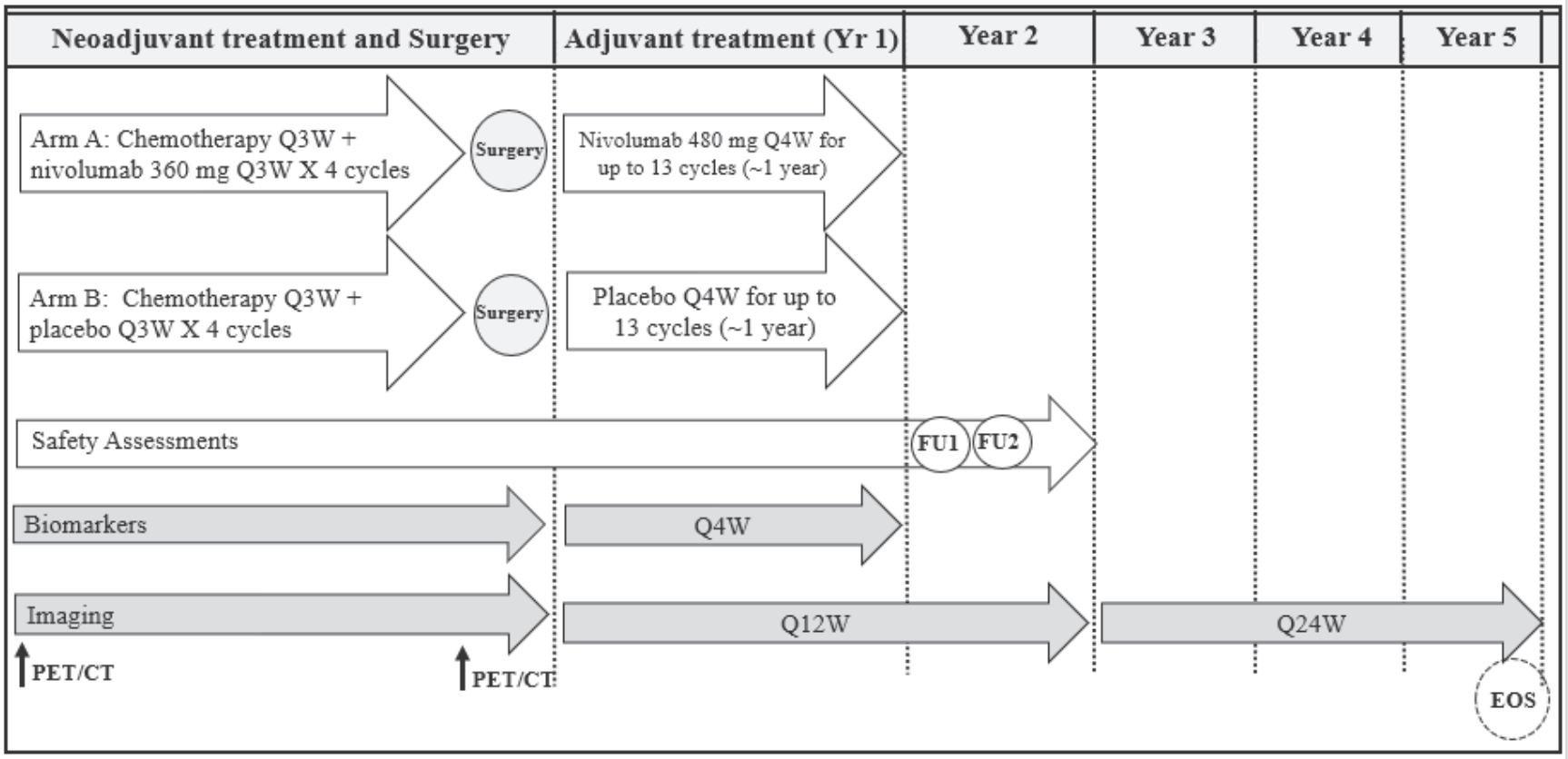
Screening phase ends with either confirmation of full eligibility and randomization or with the confirmation that the participant is a screen failure. This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure prior to randomization. If re-enrolled, the participant must be re-consented.

5.1.2 Treatment Period

The treatment phase begins with randomization after confirming all eligibility criteria have been met. The treatment period further consists of Neoadjuvant Period, Surgical Period, and the Adjuvant period.

Figure 5.1.2-1 shows a flowchart for efficacy and safety data collection during the Neoadjuvant period, Surgical period, Adjuvant period, and disease surveillance period.

Figure 5.1.2-1: CA20977T Flowchart for Efficacy and Safety Data Collection



5.1.2.1 Neoadjuvant / Pre-surgical Treatment Period

Following confirmation of eligibility, the participants will be randomized in a 1:1 ratio across the 2 arms via IRT. Treatment should begin within 3 calendar days of randomization (Figure 5.1-1).

Nivolumab 360 mg or placebo (administered IV over 30 minutes) will be combined with platinum-based doublet chemotherapy administered every 3 weeks. Combination treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Choice of platinum-based doublet regimens is made by investigator and is dependent on NSCLC histology:

Histology-based chemotherapy:

- Squamous histology:
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)
  - cisplatin (75 mg/m^2) + docetaxel (75 mg/m^2)
- Non-squamous histology:
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)
  - carboplatin (AUC 5 or AUC 6) + pemetrexed 500 mg/m^2
  - cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

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

After completing neoadjuvant treatment, participants must have a pre-surgical visit to assess status. The Neoadjuvant / Pre-surgical Treatment Period assessments are shown in Table 2-2.

5.1.2.2 Surgery

Following the completion of neoadjuvant treatment, all participants who remain operative candidates will undergo definitive surgery for NSCLC within 6 weeks of the last neoadjuvant treatment administration. In specific cases, when definitive surgery does not occur within 6 weeks of the last neoadjuvant treatment administration, definitive surgery may be permitted at a later date after discussion with the Medical Monitor. The investigator must document reason for delay of surgery in the CRF and the medical record. Participants with progressive disease or worsening of disease that precludes definitive surgery will be discontinued from treatment and will enter follow up phase.

Prior to surgery, any treatment-related toxicity should have been resolved to ≤ Grade 1 or returned to baseline (except for alopecia and fatigue). It is planned that all participants will undergo surgery following recovery from neoadjuvant therapy.

Diagnostic/Pre-surgical Evaluation and Surgical Guidelines

A participant is considered functionally operable if the following criteria are met:

- ECOG Performance Status ≤ 1
- Absence of major associated pathologies that increase the surgery risk to an unacceptable level at the discretion of the investigator or surgeon
- Pulmonary function capacity (eg, FVC, FEV1, TLC, FRC, DLco, and oxygen saturation) capable of tolerating the proposed lung resection according to the surgeon
- Absence of locally advanced, unresectable, or metastatic disease (stage IV) in the pre-treatment assessment

All participants enrolled on this study must be surgical candidates with clinical Stage IIA (> 4 cm), to resectable IIIB (T3N2 only) NSCLC. Participants will have undergone radiographic evaluation (PET/CT) indicating no evidence of distant disease and no evidence of unresectable loco-regional tumor extension (EBUS, mediastinoscopy, or thoracoscopy). Any further preoperative testing that is recommended by the surgeon or anesthesiologist will be performed as part of standard of care. Surgery for participants enrolled on this protocol will be according to generally accepted standards of care. Operative approach (VATS vs open) will be determined by the surgeon.

Accepted types of resection (with negative margins) will consist of lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy. Resections of primary tumor by segmentectomy or wedge resection will not be accepted. If PET-CT scan is positive after neoadjuvant therapy and before surgery, it is recommended that participants undergo a preoperative mediastinal evaluation by bronchoscopy/EBUS or by mediastinoscopy with pathological assessment of sites concerning for progression prior to surgery. The decision to proceed to surgery is per local guidelines and practices as long as there is no evidence of progressive disease precluding surgery. The decision to proceed with the surgery is at the discretion of treating surgeon after carefully considering the risk/benefit assessment and feasibility. For example, participants may experience an apparent radiographic progression in a solitary or in multiple nodes post treatment with the immune checkpoint inhibitor in the neoadjuvant treatment phase with pathology revealing granulomas without any evidence of tumor. The apparent radiographic progression in such cases could be attributed to nodal immune flare. Potentially curative surgery could be avoided due to failure to distinguish nodal immune flare from true disease progression. Nodal rebiopsy or restaging prior to final surgical resection is recommended if there is a high index of suspicion for true disease progression outside of the surgical field (ie, supraclavicular nodes or contralateral etc). Participants should not be denied complete resection based solely on imaging restaging following neoadjuvant therapy due to possible false positive results findings in this setting.

Therefore, pre-surgical evaluation is recommended for the following conditions:

1) Pre surgical restaging PET- CT scan reveals a new PET positive solitary or multiple nodes
2) Enlarging of preexisting, PET positive lymph node(s)

It is recommended that participants have at least 3 mediastinal and hilar lymph node stations sampled and evaluated during surgery. Systematic sampling is defined as removal of at least 1 representative lymph node at specified levels. MLND entails resection of all lymph nodes at those same levels.

The following sampling for MLND locations are required, when clinically feasible:

- For right-sided tumor: Levels 4, 7, 9R, 10R and 11R
- For left-sided tumor: Levels 5 and/or 6; 7, 9L, 10L, and 11L

A clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node areas is required. Pathologists must examine the resected specimen according to SOC practices. To the extent feasible, all excised lymph nodes should be identified, processed, and examined microscopically for the presence or absence of metastasis.

Pathology slides (comprehensive guidelines for specimen handling and identification of the tumor/tumor bed and lymph nodes are described in the pathology manual) from the surgical resection must be submitted to blinded independent pathology review (BIPR) at a central site to confirm whether a pCR or major pathologic response (MPR) was achieved.

Tumor tissue from the surgical resection must also be submitted for exploratory biomarker analyses. Details will be found in the CA20977T Laboratory Manual.

Prior to surgery, participants with disease progression that precludes surgery must be discontinued from study treatment and tumor assessments and will enter follow up phase.

5.1.2.3 Participants not receiving surgery

Some participants who have completed neoadjuvant therapy (4 or fewer cycles) may develop medical conditions due to adverse events or other causes that, in the opinion of the investigator, precludes them from safely undergoing surgery. The reasons for not proceeding with surgery should be clearly documented in the medical records and the CRF.

For participants not receiving surgery, the decision for subsequent adjuvant treatment or treatment discontinuation will be based on criteria for disease recurrence or disease progression, as defined in Section 9.1.1 and Section 9.1.2.

- **If a participant does not receive surgery and meets the definition of an event,** study treatment must be discontinued and participant should move to Follow-up care. This decision must be clearly documented in the medical records and in the CRF.
- **If a participant does not receive surgery and does not meet the definition of an event,** adjuvant treatment may be initiated upon approval from Medical Monitor or designee. This decision must be clearly documented in the medical records and in the CRF.

Participants who do not have surgery will be unable to submit tissue for pCR, but will be able to submit samples for biomarker analyses. See Section 9.8.

5.1.2.4 Postoperative radiotherapy as Standard of Care (SOC)

Following surgery, participants in both treatment arms may receive post-operative radiation therapy (PORT) at the discretion of the investigator per SOC and local institutional standards under the following conditions:

- Positive margins post-surgery
- N 2 disease post-surgery
- Macroscopic residual tumor

Investigators should document the reason for choosing radiation in the medical records and the CRF.

Postoperative radiotherapy should not commence until post surgical adverse events or treatment-related toxicity have returned to baseline or resolved to ≤ Grade 1 (exceptions for fatigue and alopecia).

As radiation may interfere with imaging interpretation, efforts should be made to schedule radiotherapy so that scheduled tumor assessments do not cross over into the radiation period.

PORT must be completed before initiating adjuvant treatment in both arms. The rebaseline tumor assessment after surgery must be done after PORT has been completed and within 1 week before initiating adjuvant treatment.

5.1.2.5 Post surgical/Preadjuvant Evaluation

Participants receiving Surgery: All AEs, serious adverse event (SAE), and drug-related AEs resulting in surgical delays and post surgical complications will be collected. Peri-operative complications, including a delay in planned surgery, pneumonitis, ARDS, re-admission to the Intensive Care Unit, atrial fibrillation or other SVTs, potential immune-related toxicities, and post operative complications will be collected. Surgical complications occurring within 90 days of surgery will be documented and followed until resolution.

The first tumor assessment should occur within 1 week prior to adjuvant treatment. Subsequent assessments should occur every 12 weeks (± 7 days) for up to and including 108 weeks (approximately 2 years) following first dose of adjuvant treatment, then every 24 weeks (± 14 days) for up to and including Week 276 (approximately 5 years) until disease recurrence or disease progression is confirmed by blinded independent central review (BICR) and, in addition, continue until investigator-assessed distant metastasis.

All assessments should be collected as per Table 2-3 before receiving adjuvant treatment.

Participants not receiving Surgery: All AEs and SAEs related to neoadjuvant treatment will be collected. Participants that do not undergo surgery will continue to have tumor assessments every 12 weeks (± 7 days) for up to and including 108 weeks (approximately 2 years) following on the

presurgery PET-CT scan, then every 24 weeks (± 14 days) for up to and including Week 276 (approximately 5 years) until disease progression or disease recurrence is confirmed by BICR and, in addition, continue until investigator-assessed distant metastasis.

5.1.2.6 Adjuvant Treatment (Post surgical treatment) [Year 1]

Adjuvant treatment (after surgery) should begin within 90 days from the date of definitive surgery. All participants should have a post surgery visit (30 to 90 days post definitive surgery) and re-baseline restaging imaging prior to beginning adjuvant treatment (within 1 week prior to adjuvant treatment) to rule-out recurrence.

All toxicities associated with neoadjuvant therapy must have been resolved prior to adjuvant treatment (exceptions for fatigue, alopecia, and neuropathy). All assessments (including post surgery/preadjuvant visit) must be performed prior to adjuvant treatment.

After the surgical phase, participants will continue to receive treatment in the assigned treatment arms. Each treatment cycle lasts for 28 days:

Arm A adjuvant treatment: Participants will receive nivolumab 480 mg flat dose IV Q4 weeks maximum treatment duration of 13 cycles (for approximately 1 year).

Arm B adjuvant treatment: Participants will receive placebo Q4 weeks IV for a maximum treatment duration for 13 cycles (for approximately 1 year).

Participants will complete 13 cycles (approximately 1 year) of adjuvant treatment except in the event of disease progression, disease recurrence, death, unacceptable toxicity, symptomatic deterioration, investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant being lost to follow-up, end of the study, or BMS decision to terminate the study. All assessments should be collected as per Table 2-3.

5.1.3 Disease Surveillance Assessments from Year 2 to Year 5 and Safety Follow-up Visits

After completing treatment with protocol specified adjuvant study treatment, participants will have follow-up assessments (FU1 and FU2) and disease surveillance (Year 2 through year 5).

Participants who receive study treatment and discontinue treatment for unacceptable toxicity will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication. During the follow-up visit, participants will have assessments and continue disease surveillance as described in Table 2-4.

5.1.4 Disease Progression/Recurrence

If a participant received study treatment and has disease recurrence/progression precluding surgery in neoadjuvant phase or BICR-confirmed disease progression or worsening of disease after adjuvant treatment, the participant will complete the 2 safety Follow-up visits and then enter into the survival follow-up phase (Table 2-4). At BICR-confirmed disease progression, the investigator may request PD-L1 status from screening.

5.1.5 Data Monitoring Committee and Other External Committees.

An independent Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio in protocol. Following review, the DMC will recommend continuation, modification, or discontinuation of this study based on reported safety data. Representatives of the Sponsor will serve only as coordinators of the committee, without having full member responsibilities or privileges. In addition, the Sponsor will independently review safety data in a blinded manner during the conduct of this trial to ensure that any safety issues are identified and addressed. Available efficacy data will also be reviewed by the DMC during the conduct of the study. Details of the DMC responsibilities and procedures will be specified in the DMC charter.

5.2 Number of Participants

Approximately 452 participants will be randomized in a 1:1 ratio to treatment with either Arm A or Arm B. Assuming a 40% screening failure rate, it is estimated that approximately 750 participants will be enrolled in order to have approximately 452 participants randomized.

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

5.4 Scientific Rationale for Study Design

The incorporation of nivolumab to neoadjuvant chemotherapy with adjuvant maintenance may increase the pathological complete response rate (pCR) and prolong event-free survival (EFS) and increase overall survival (OS) as compared with neoadjuvant chemotherapy in participants with newly diagnosed resectable NSCLC.

The early-stage (II-IIIB) NSCLC represents a population of high unmet need with a 5-year survival rate of 25-50%. The current available standard of care (SOC) only provides a 5% absolute improvement in 5-year overall survival (OS). The SOC comprises adjuvant or neoadjuvant platinum-based doublet chemotherapy for patients with operable stage IB-IIIA NSCLC or chemoradiation for patients with unresectable stage IIIA/B NSCLC. Follow-up of adjuvant trials are long and may require decades before a new treatment is introduced into clinical practice. Preoperative or neoadjuvant chemotherapy has been assessed in a number of trials for patients with operable NSCLC. A meta-analysis based on 7 trials involving 988 patients suggested that neoadjuvant chemotherapy improved OS when given preoperatively in a similar magnitude to those observed with adjuvant chemotherapy. Neoadjuvant therapy offers the possibility for the identification of surrogate clinical and biological markers that may correlate with response to therapy and a potential long-term outcome. Studies that address the role of preoperative chemotherapy have found chemotherapy compliance to be favorable in the preoperative setting. Randomized trials are currently on-going to explore the potential benefit of nivolumab in the neoadjuvant, adjuvant and locally advanced unresectable NSCLC setting. In addition, the safety

and efficacy profile of neoadjuvant nivolumab monotherapy or in combination (nivolumab plus chemotherapy) are being evaluated in ongoing trials.

5.4.1 Rationale for Study Design

Standard of care treatment using 3 different treatment modalities (surgery, systemic therapy, and radiotherapy) is used to treat participants with locally advanced NSCLC Stage II to IIIB. Depending on participant status and clinical outcomes from neoadjuvant treatment, participants may subsequently undergo surgical resection. The efficacy of periadjuvant immunotherapy has not been fully evaluated in participants with locally advanced NSCLC. Therefore, in addition to SOC platinum-based doublet chemotherapy with surgical resection, participants will receive nivolumab/ nivolumab placebo before surgery (neoadjuvant) and after surgery (adjuvant). The use of placebo as a control will allow for a more objective evaluation of the efficacy and safety of nivolumab. A double blinded, placebo controlled study is ethically justified as participants will receive SOC treatment and potentially, participants receiving immunotherapy may demonstrate clinical benefit by adding immunotherapy in this periadjuvant setting.

5.5 Justification for Nivolumab Dose

Nivolumab monotherapy has been extensively studied in NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057 with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of participants in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK.

Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time. A flat dose of 360 mg every 3 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants.

A PPK model predicted overall nivolumab exposures across participants with a wide range of body weight (35-160 kg) for a 360 mg every 3 weeks flat dose to be similar to that from 3 mg/kg every 2 weeks. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures from these regimens are maintained well below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose.

Nivolumab 5 or 10 mg/kg every 3 weeks plus platinum-based chemotherapy was evaluated in CA209012 and deemed to be tolerable. In addition, nivolumab 360 mg every 3 weeks plus platinum-based chemotherapy is further being evaluated on several global randomized phase 3 trials including CA209227 and has been safe and tolerable.

After surgery, participants will receive nivolumab 480 mg every 4 weeks (Q4W), which provides a more convenient dosing regimen for participants. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with 240 mg Q2W and is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed exposures at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants or legal authorized representatives where locally allowed (see Appendix 2). Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

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

2) Type of Participant and Target Disease Characteristics

a) Participants with suspected or histologically confirmed Stage IIA (> 4 cm) to IIIB (T3N2) NSCLC (per the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th Edition[22]) with disease that is considered resectable.

Note: Participants must be evaluated by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc) during screening.

Note: Participants with N3 nodal disease are not eligible. Participants with resectable T4 tumor size with Stage IIIA or IIIB disease must be reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc). The review of the multidisciplinary team must be documented in CRF and medical record.

b) No brain metastasis

c) Participant must be deemed eligible for complete resection and must agree to undergo standard of care surgery for complete resection of NSCLC after neoadjuvant therapy

d) Treatment-naive for NSCLC (no prior systemic anti-cancer treatment)

e) Ability to provide surgical or biopsy tumor tissue for biomarkers (eg, whole exome sequencing, PD-L1 testing, etc) See Section 9.8.

i) All participants must have tissue submitted to a central laboratory during screening. Either FFPE (preferred) tissue block or 5-10 unstained tumor tissue slides, 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.

f) Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1

3) Age and Reproductive Status

a) Males and Females, ≥ 18 years

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatments and after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the study drug to undergo approximately 5 half-lives. WOCBP must agree to follow instructions for method(s) of contraception for 6 months or longer as per the local regulation and approved product label after the last dose of study treatment (for nivolumab and chemotherapy regimens specified as study treatment in the protocol).

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 treatments and after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the study drug to undergo approximately 5 half-lives). Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

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

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

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with EGFR mutation regardless of mutation type are excluded. Non-squamous tumors with unknown EGFR mutation status must be tested for EGFR mutation. Use of a

FDA-approved or local Health Authority-approved test (tissue or blood) is strongly encouraged.

b) Participants with known ALK mutations

c) Participants with Grade ≥ 2 peripheral neuropathy

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 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) Participants with interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment) that may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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

h) 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.

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

j) Participants with serious or uncontrolled medical disorders.

2) Prior/Concomitant Therapy

a) Any previous anti-cancer treatment including cytotoxic, IO treatment, targeted agents, or radiotherapy for NSCLC

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

c) Participants who have received a live/attenuated vaccine within 30 days of randomization

d) Prior treatment with any 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

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
e) Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)
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 < 3.0x 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).

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to platinum-containing compounds, pemetrexed, paclitaxel, docetaxel, or other study drugs and their components

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

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

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 re-registered in the IRT for new patient ID allocation.

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.

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:

- Nivolumab
- Carboplatin
- Cisplatin
- Docetaxel
- Paclitaxel
- Pemetrexed
- Normal saline or dextrose (eg, 5% dextrose in water) will be used as nivolumab-placebo and will not be provided by BMS/Sponsor.

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

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

- Refer to the pharmacy manual for instructions on handling and labeling to preserve the blind.

Table 7-1: Study treatments for CA20977T

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection/Nivolumab[a]	100 mg (10 mg/mL)	IP	Open-label	Clear to opalescent, colorless to pale yellow liquid. Few particulates may be present.	2 to 8° C. Protect from light and freezing
Carboplatin Solution for Injection [b]	450 mg/vial (10 mg/mL)	IP	Open-label	Clear, colorless or slightly yellow solution.	Product should be stored as per market product conditions.
Cisplatin Concentrate for Solution for Infusion [b]	100 mg/vial (1 mg/mL)	IP	Open-label	Clear, colorless solution	Product should be stored as per market product conditions.
Docetaxel Concentrate for Solution for Infusion [b]	80 mg (10 mg/ml)	IP	Open label	Clear, colorless to pale yellow solution	Product should be stored as per market product conditions.
Paclitaxel Solution for Injection [b]	100 mg/vial (6 mg/mL)	IP	Open-label	Clear, colorless or slightly yellow viscous solution.	Product should be stored as per market product conditions.
Pemetrexed Powder for Concentrate for Solution for Infusion [b]	500 mg/vial	IP	Open-label	White to either light yellow or green-yellow lyophilized powder	Product should be stored as per market product conditions.

[a] May be labeled as either “BMS-936558-01” or “nivolumab”

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

7.1 Treatments Administered

Table 7.1-1 describes the selection and timing of dose for each participant.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-936558-01 Nivolumab[a]	10 mg/mL	360 mg on Day 1 of a 3-week cycle for up to 4 cycles as neoadjuvant therapy 480 mg on Day 1 of a 4-week cycle for up to 13 cycles (approximately 1 year) as adjuvant therapy	IV
Carboplatin[23]	10 mg/mL	AUC 5 or AUC 6 on Day 1 of a 3-week cycle for up to 4 cycles [a,b]	IV.
Cisplatin[24]	1 mg/mL	75 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles [a]	IV
Docetaxel[25]	10 mg/mL	75 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles [a]	IV
Paclitaxel (Taxol PI)[26,27]	6 mg/mL	175 mg/m^2 or 200 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles [a]	IV
Pemetrexed[28]	500 mg/vial	500 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles [a]	IV

[a] Participant in the nivolumab placebo arm will receive normal saline or dextrose following the same dosing schedule.

[b] Carboplatin is initiated at a dose of AUC 5 or 6

7.1.1 Neoadjuvant Treatment

7.1.1.1 Nivolumab or Placebo during Neo-adjuvant Treatment

Participants will be randomized to receive nivolumab/nivolumab placebo as neoadjuvant treatment.

Participants are to begin study treatment within 3 calendar days of randomization. Participants will receive nivolumab at a dose of 360 mg as a 30-minute infusion or placebo on Day 1 of every 3 weeks cycle (± 3 days) for 4 cycles. There will be no dose escalations or reductions of nivolumab allowed. Neoadjuvant treatment will be given for up to 4 cycles until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants may be dosed no less than 18 days from the previous dose during Q3W cycles.

Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Dose of nivolumab may be interrupted, delayed, or discontinued depending on how well the participants tolerates the treatment. Dose delay criteria can be found in Section 7.4.2.1 and discontinuation criteria can be found in Section 8.1.1. Criteria to resume treatment can be found in Section 7.4.4.1.

Refer to instructions below for instructions for doublet chemotherapy administration in Section 7.1.1.2 and Section 7.1.1.3.

7.1.1.2 Platinum-based Doublet Chemotherapy Regimens

Participants are to begin study treatment within 3 calendar days of randomization. Participants will receive nivolumab/nivolumab placebo, followed by chemotherapy on day 1 of every 3 weeks cycle. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants are to receive nivolumab 360 mg IV (or nivolumab placebo) plus histology dependent platinum-based doublet chemotherapy in 3-week cycles for 4 cycles.

Histology-based chemotherapy:

- Squamous histology:
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)
  - cisplatin (75 mg/m^2) + docetaxel (75 mg/m^2)
- Non-squamous histology:
  - carboplatin (AUC 5 or AUC 6) + pemetrexed (500 mg/m^2)
  - cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2)
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)

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

Dosing calculations for chemotherapy should be based on the body surface area calculation assessed as per standard of care. The dose should remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight All doses should be rounded up or to the nearest milligram or per institutional standard. When study drugs (nivolumab and chemotherapy) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the chemotherapy infusion. The time in between infusion of nivolumab and chemotherapy is expected to be approximately 30 minutes but may be more or less depending on the situation

If any adverse event meeting the dose delay criteria for chemotherapy is thought to be related to one individual chemotherapy agent only in the platinum-based doublet chemotherapy regimen, then that individual chemotherapy agent alone may be omitted for that cycle while the other agents (nivolumab and the other chemotherapy agent) are administered. If the dose delay criteria for nivolumab or both platinum-based doublet chemotherapy agents are met, dosing of nivolumab and both chemotherapy agents should be delayed.

7.1.1.3 Dosing Information for Platinum-based Doublet Chemotherapy

Pemetrexed/Cisplatin: Pemetrexed will be administered at a dose of 500 mg/m^2 as a 10 minute or per institutional standard IV infusion and cisplatin will be administered at a dose of 75 mg/m^2 as a 120-minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculation for pemetrexed should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up or to the nearest milligram per institutional standard.

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

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to Section 7.4.1. Dose delay criteria can be found in Section 7.4.2.2, and discontinuation criteria can be found in Section 8.1.2. Criteria to resume treatment can be found in Section 7.4.4.2. Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Pemetrexed should not be administered if the calculated CrCl is < 45 mL/min.

Participants with pre-existing hearing impairment should not receive cisplatin and should receive carboplatin-based regimen.

Premedications for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg twice daily on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1,000 mcg daily should be given starting approximately 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed. See details below regarding administration of cisplatin.

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.

Docetaxel /Cisplatin: Docetaxel will be administered at a dose of 75 mg/m^2 as a 60 minute IV infusion on Day 1 of a treatment cycle every 3 weeks (21 days) or per institutional standard IV infusion followed by cisplatin which will be administered at a dose of 75 mg/m^2 over 60 -minute IV infusion or per institutional standard on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculation for docetaxel should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up or to the nearest milligram per institutional standard.

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

Participants with pre-existing hearing impairment should not receive cisplatin and should receive carboplatin-based regimen. For participants with squamous histology who have preexisting hearing impairment, the carboplatin + paclitaxel regimen should be used.

Doses of docetaxel and/or cisplatin may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to Section 7.4.1. Dose delay criteria can be found in Section 7.4.2.2, and discontinuation criteria can be found in Section 8.1.2. Criteria to resume treatment can be found in Section 7.4.4.2.

Paclitaxel/Carboplatin: Paclitaxel will be administered at a dose of 175 or 200 mg/m^2 as a 180 minute or per institutional standard IV infusion and carboplatin will be administered at a dose of AUC 5 or 6 as a 30-minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles.

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

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

Carboplatin dose (mg) = Target AUC x (CrCl [ml/min] + 25)

Creatinine clearance (CrCl) calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight.

NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards

Doses of paclitaxel and/or carboplatin may be modified, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to Section 7.4.1. Dose delay criteria can be found in Section 7.4.2.2, and discontinuation criteria can be found in Section 8.1.2. Criteria to resume treatment can be found in Section 7.4.4.2.

Premedications for use with paclitaxel: Oral or IV corticosteroid should be given prior to paclitaxel according to local standard. Such premedication may consist of oral dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel administration. Oral or IV diphenhydramine 50 mg (or its equivalent) and an H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion. 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 per local standards of care.

All participants should be carefully monitored for infusion reactions during the paclitaxel administration. Participants should be treated in a facility with the necessary medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

See below for the details regarding administration of carboplatin.

For participants who do not receive cisplatin-based regimen at C1D1, the investigator should document the reason for not choosing a cisplatin-based regimen in the CRF and medical records.

For participants who are unable to tolerate cisplatin, the investigator should document the reasons for intolerability. If the investigator would like to use a carboplatin-based regimen as specified in the protocol, the investigator should document reasons in CRF and medical record.

Pemetrexed/Carboplatin: Pemetrexed will be administered at a dose of 500 mg/m2 as a 10 minute or per institutional standard IV infusion and carboplatin will be administered at a dose of AUC 5 or 6 as a 30-minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculation for pemetrexed should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within

10% of the baseline weight or prior dose weight. All doses should be rounded up or to the nearest milligram per institutional standard.

Carboplatin should be given following pemetrexed per institutional standard on Day 1 of each cycle. The carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC x (CrCl [ml/min] + 25)

Creatinine clearance (CrCl) calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight.

NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to Section 7.4.1. Dose delay criteria can be found in Section 7.4.2.2, and discontinuation criteria can be found in Section 8.1.2. Criteria to resume treatment can be found in Section 7.4.4.2. Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Pemetrexed should not be administered if the calculated CrCl is < 45 mL/min.

Premedications for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg twice daily on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1,000 mcg daily should be given starting approximately 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed.

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.

For All Arms Containing Chemotherapy: Participants should begin study treatment within 3 calendar days of randomization. Doses of chemotherapy may be interrupted, delayed, or

discontinued depending on how well the participants tolerates the treatment. If a dose is delayed for any reason, participants should be dosed no less than 18 days from the previous dose.

Premedications: 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.

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

7.1.2 Nivolumab or Placebo for Adjuvant Treatment

Participants will follow previous randomization and will receive nivolumab or placebo as adjuvant treatment.

After surgery, participants will receive nivolumab at a dose of 480 mg as a 30-minute infusion or placebo on Day 1 of every 4 weeks cycle (± 3 days) for up to 13 cycles (approximately 1 year) until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 25 days from the previous dose during Q4W cycles.

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. The following information is required for participant randomization:

- Participant number
- Year of birth
- Tumor histology (squamous vs non-squamous)
- NSCLC stage (II vs III)
- PD-L1 tumor expression status (PD-L1 positive vs PD-L1 negative vs PD-L1 indeterminate/not evaluable), analyzed by the central laboratory vendor and transferred to the IRT

The exact procedures for using the IRT will be detailed in the IRT manual. Study treatment will be administered at the study visits as listed in the Schedule of Activities (Section 2).

7.3 Blinding

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

Treatment allocation (nivolumab versus placebo) will only be available through the IRT to an unblinded pharmacist or other individual(s) who will be responsible for the dispensing of blinded study drug. This (these) individual(s) will be unblinded to study drug identification but will not be involved in any other aspect of study conduct.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is IRT (refer to the IRT manual for further instructions).

In cases of accidental unblinding, contact the BMS unblinded study team (as described in the Onsite Investigator File) and NOT the Medical Monitor) and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the Interactive Response Technology (IRT) and is capable of breaking the blind through the IRT system without prior approval from sponsor. Following the unblinding the Investigator shall notify the medical monitor and/or study director.

Additionally, designated staff in the Bristol-Myers Squibb Bioanalytical Sciences department (and/or a designee in the external bioanalytical laboratory) may receive the randomization

treatment assignments in order to minimize unnecessary bioanalytical analysis of PK and immunogenicity samples.

7.4 Dosage Modification

7.4.1 Dose Reductions for Platinum-based Doublet Chemotherapy

Dose reductions of platinum-based doublet chemotherapy may be required and will be performed according to Table 7.4.1-1. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles. The dose reductions for each agent in the platinum-based doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.1-1: Dose Reductions for Platinum-based Doublet Chemotherapy

Dose Level	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel	Docetaxel
Starting dose	500 mg/m²	75 mg/m²	AUC 5 or 6	175 or 200 mg/m²	75 mg/m²
First dose reduction	75% of the starting dose	75% of the starting dose	AUC 4 or 5	150 mg/m²	75% of the starting dose
Second dose reduction	50% of the starting dose	50% of the starting dose	AUC 3 or 4	100 mg/m²	50% of the starting dose
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

NOTE: Follow local regulations if they are different than what appears in this table.

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

7.4.1.1 Platinum-based Doublet Chemotherapy - Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4) are summarized in Table 7.4.1.1-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for platinum-based doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the platinum-based doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 7.4.1.1-1: Dose Modifications for Hematologic Toxicity (based on Nadir Counts)[a]

Toxicity	Pemetrexed	Cisplatin	Carboplatin	Paclixatel	Docetaxel
Neutrophil Count Decreased					
Grade 4 (< 500/mm^3 or < 0.5 x 10^9/L)	Reduce one dose level and consider prophylactic GCSF in subsequent cycles	Reduce one dose level and consider prophylactic GCSF in subsequent cycles	Reduce one dose level and consider prophylactic GCSF in subsequent cycles	Reduce one dose level and consider prophylactic GCSF in subsequent cycles	Reduce one dose level and consider prophylactic GCSF in subsequent cycles
Platelet Count Decreased					
Grade 3 (25,000 to < 50,000/mm^3; 25.0 to < 50.0 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 (< 25,000/mm^3; < 25.0 x 10^9/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Hemoglobin					
Grade 2 (< 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 - 80 g/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 3 (< 8.0 g/dL; < 4.9 mmol/L, < 80 g/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 (Lifethreatening consequences)	Hold drug	Hold Drug	Hold Drug	Hold drug	Hold drug

[a] If local standard for dose adjustments differ from those outlined, please discuss with the Medical Monitor.

7.4.1.2 Platinum-based Doublet Chemotherapy - Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for platinum-based doublet chemotherapy for non-hematologic toxicities during treatment are summarized in Table 7.4.1.2-1. Participants experiencing any of the toxicities during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 7.4.2.2) and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the platinum-based doublet chemotherapy regimen are not linked and may be reduced independently, as summarized in Table 7.4.1.2-1.

Table 7.4.1.2-1: Dose Modifications for Non-hematologic Toxicity

Toxicity	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel	Docetaxel
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	Reduce one dose level	No change	No change	Reduce one dose level	Reduce one dose level
Allergic reaction[a] Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	Reduce one dose level[b]	No change	Reduce one dose level	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	Discontinue if creatinine clearance < 45 mL/min	Discontinue	Discontinue if creatinine clearance < 20 mL/min	No change	Reduce one dose level if creatinine clearance < 30 mL/min
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

Note: If local standard for dose adjustments differ from those outlined, please discuss with the Medical Monitor. Please see local drug label for additional adjustments.

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

[b] When given with pemetrexed, cisplatin should be reduced 2 dose levels (ie, by 50% for Grade 2 neuropathy).

7.4.2 Dose Delay

7.4.2.1 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 (see Section 8.1.1).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.2.2 Dose Delay Criteria for Platinum-based Doublet Chemotherapy

Dosing of both drugs in the platinum-based doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) ≤ 1500/µL
- Platelets < 100,000/mm^3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay.
  - If a participant has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
  - If total bilirubin is > ULN, delay docetaxel administration

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only 1 particular agent in the platinum-based doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 7.4.1 to determine if dose reduction of the resumed agent is required.

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

7.4.3 Treatment of Nivolumab-related Infusion Reactions

Since nivolumab contains 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 National Cancer Institute (NCI) common terminology criteria for adverse event (CTCAE, Version 4) 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 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 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 will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF).

- 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. 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. Begin an IV infusion of normal saline and treat the participant t 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 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).

7.4.4 Criteria to Resume Dosing

7.4.4.1 Criteria to Resume Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- 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 who delay study treatment due to any Grade 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, which is assessed by the investigator not to be related to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The Medical Monitor should be consulted prior to resuming nivolumab in such participants.

7.4.4.2 Criteria to Resume Treatment with Chemotherapy

- Participants may resume treatment with chemotherapy when the ANC returns to 1500/µl. the platelet count returns to 100,000/mm^3, and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue).
- If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 8 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming chemotherapy treatment, follow the dose reduction recommendations in Section 7.4.1.

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 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 unblinded pharmacist and/or product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

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

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

The unblinded pharmacist will obtain treatment assignment by IRT and prepare blinded drug (nivolumab or placebo).

Please refer to the current version of the appropriate IB, Pharmacy Manual and Appendix 2, for complete storage, handling, dispensing and final disposition of unused study treatment.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and case report form (CRF). Drug accountability should be reviewed by the unblinded pharmacist at each visit to confirm treatment compliance.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2
- Any additional, concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC) outside of study treatment.
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- 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.
- **Strong** CYP3A4 inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, etc) must not be administered with docetaxel. If strong CYP3A4 inhibitors cannot be discontinued, another chemotherapy regimen must be used.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Participants may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria (Section 6.2) describe other medications that are prohibited during this study. There are no prohibited therapies during the post treatment follow-up phase.

7.7.2 Other Restrictions and Precautions

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

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

7.7.2.1 Imaging Restriction and Precautions

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

contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participant with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image 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 the nivolumab 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
- 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 as a participant. Strict conditions apply and BMS approval is required.)

8.1.1 Nivolumab Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, 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. Grade ≥3 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 will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/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, 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 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, 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.

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.

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

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

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

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

8.1.2 Platinum-based Doublet Chemotherapy Dose Discontinuation

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

- Any Grade ≥ 3 peripheral neuropathy
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10x ULN for > 2 weeks
  - AST or ALT > 10x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in creatinine clearance to < 50 mL/min (using the Cockroft Gault formula) requires discontinuation of cisplatin. The other chemotherapeutic agent may be continued or the regimen may be switched to a carboplatin-based regimen as specified in the

protocol. The investigator should discuss this with and obtain approval from the Medical Monitor prior to switch.

- Pemetrexed should be discontinued when creatinine clearance to < 45 mL/min (using the Cockroft Gault formula)
- Any drug-related adverse event which recurs after 2 prior dose reductions for the same drug-related adverse event (as specified in Section 7.4.1.1 and Section 7.4.1.2) requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related adverse event which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 8 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Cystoid macular edema (CME) diagnosed by ophthalmologic examination requires discontinuation
- Note: CME has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. If CME is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued platinum-based doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.

If the investigator is unable to determine whether an adverse event is due to nivolumab or to platinum-based doublet chemotherapy, then all drugs must be discontinued.

8.1.3 Post Study Treatment Follow-up

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Table 2-4 until death or the conclusion of the study.

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

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities.

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

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary 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.

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 investigator. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

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

Participants will be followed for survival every 3 months via in person or by telephone contact after the participants have discontinued study drug treatment. All randomized participants will be followed for survival.

9.1.1 Definition of Events in EFS

EFS is defined as the length of time from randomization to any of the following events: progression of disease or worsening of disease that precludes surgery, if surgery is attempted but gross resection is abandoned due to unresectable tumor or worsening of disease, progression or recurrence of disease without surgery, or death due to any cause. Details on EFS events are provided below:

- Disease progression or worsening of disease that precludes surgery (as determined by Investigator)
- If surgery is possible but not performed for other reasons (participant refuses or worsening of medical condition), then the participant may continue on study treatment and will be considered to have an EFS event if and when there is RECIST v1.1 defined progression (requires BICR confirmation)
- If surgery is attempted but gross resection is abandoned, due to unresectable tumor or worsening of disease, then that will be considered an EFS event (Investigator assessment collected on the eCRF surgery page) [event date = surgery date]. If surgery is attempted but gross resection is abandoned for reasons other than unresectable tumor or worsening of disease, this will not be considered an EFS event. The participant may continue on study treatment and will be considered to have an EFS event if and when there is RECIST v1.1 defined progression (requires BICR confirmation).
- If surgery is completed with unequivocal gross residual disease (visible on imaging), then the participant may continue on study treatment and will be considered to have an EFS event if and when there is RECIST v1.1 defined progression (requires BICR confirmation)
- If surgery is completed with no or only microscopic residual disease (positive margins, not visible on imaging), then the participant will continue on study and will be considered to have an EFS event if and when radiographically visible recurrence occurs (requires confirmation by BICR) or by biopsy.
- Local or distant recurrence or new tumor confirmed by BICR or biopsy
- Death due to any cause

9.1.1.1 Definition of Disease Recurrence

Disease recurrence will be defined as any unequivocal evidence of new lung cancer lesions that are detected after surgery. Biopsy should be employed where required to prove recurrence. In cases where recurrence is equivocal and biopsy cannot be performed or were not diagnostic, the participant may continue treatment and imaging of suspect lesions should be repeated in 4-8 weeks (Section 9.1.2.4**).**

The first post surgery assessment will occur within 90 days after surgery and prior to beginning post surgery IO therapy for Arms A and B. Participants who have new LNs of ≥ 10 mm in short axis or with growth of ≥ 5mm (eg, 9 mm LN grows to 14 mm) have findings of other new, unequivocal non-nodal lesions will be considered as having recurrence. Confirmation of recurrence must be attempted as described in Section 9.1.1.2

Tumor may recur in the following sites:

- Local recurrence (ie, ipsilateral [disease in same lung])
- Distant recurrence (any new non-local recurrence)

9.1.1.2 Definition of Disease Progression

All participants will be followed by imaging for disease progression until BICR-confirmed unequivocal progression per RECIST 1.1.

9.1.1.3 Definition of pCR

The pCR rate is defined as the number of randomized participants with absence of residual viable tumor in lung and lymph nodes as evaluated by blinded independent pathology review (BIPR), divided by the number of randomized participants for each treatment group.

9.1.1.4 Definition of MPR

MPR is defined as number of randomized participants with ≤10% residual viable tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group.

9.1.2 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA20977T Imaging Manual provided by the central imaging vendor.

Imaging assessments will occur in accordance with the Schedule of Activities in Section 2.

9.1.2.1 Neoadjuvant and Pre-Surgical Imaging

PET-CT with contrast is required at Screening for all participants and should be acquired up to 45 days prior to randomization. If the CT component of a PET-CT is not of sufficient diagnostic quality for RECIST 1.1 assessment, a separate CT with contrast of the chest, abdomen, pelvis and other suspected areas (in addition to the PET-CT) is required. If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable.

A preoperative PET-CT with contrast should be acquired at least 14 days after last neoadjuvant dose and before surgery. If the CT component of a PET-CT is not of sufficient diagnostic quality for RECIST 1.1 assessment, a separate CT with contrast of the chest, abdomen, pelvis and other suspected areas (in addition to the PET-CT) is required. If CT with contrast of the abdomen, pelvis and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable.

Participants that do not undergo surgery will continue to have tumor assessments every 12 weeks (± 7 days) for up to and including 108 weeks (approximately 2 years) following on the presurgery PET-CT scan, then every 24 weeks (± 14 days) for up to and including Week 276 (approximately 5 years) or until BICR-confirmed disease progression or recurrence and, in addition, continue until investigator-assessed distant metastasis.

9.1.2.2 Post Surgical / Preadjuvant Restaging and Adjuvant Imaging

Post surgical and/or preadjuvant restaging using contrast-enhanced CT chest, as well as pre and post contrast-enhanced CT of abdomen, pelvis, and other suspected areas should occur within 7

days prior to first dose of adjuvant treatment. If CT with contrast of the abdomen, pelvis and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable.

Radiographic assessments will continue every 12 weeks (± 7 days) for up to and including 108 weeks (approximately 2 years) following first dose of adjuvant treatment, then every 24 weeks (± 14 days) for up to and including Week 276 (approximately 5 years) until disease recurrence or disease progression is confirmed by blinded independent central review (BICR) and, in addition, continue until investigator-assessed distant metastasis.

9.1.2.3 Methods of Measurement

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

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

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

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT with intravenous contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable. Bone scans may be collected per local standards, as clinically indicated.

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

During the neoadjuvant therapy period, participants should have 2 PET-CT scans, ideally with IV contrast, of skull base through the mid-thigh performed:

- within 45 days of randomization, and then
- at least 14 days after last neoadjuvant dose and before planned surgery to assess for clinical response.

A separate contrast enhanced CT of the chest, abdomen, pelvis, and other known/suspected areas is required if the CT component of a PET-CT is not of sufficient diagnostic quality of RECIST 1.1 measurements. If CT with contrast of the abdomen, pelvis, and all other known and/or suspected sites of disease is contraindicated, then a MRI is acceptable.

9.1.2.4 BICR Assessment of Progression

Sites should submit all scans to BICR as performed on a rolling basis, preferably within 5 days of scan acquisition, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression or recurrence 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 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 or recurrence is not confirmed by BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until the BICR confirmed progression or recurrence and, in addition, continue until investigator-assessed distant metastasis. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 5.1.4 until progression or recurrence is confirmed by BICR.

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

9.1.3 Blinded Independent Pathology Review

Independent pathology review will be established for central review and confirmation of endpoints. Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor for biomarker studies is mandatory. Specimen sampling for histopathologic analysis should be performed within 72 hours of the surgical procedure. Sections will be used for central pathology review assessing pathologic response. All H&E slides prepared from the specimens that are reviewed locally must be sent for central pathology review. Diagnostic H&E slides are preferred, but recut sections from all the tissue blocks are acceptable. Sites will be trained prior to enrolling the first study participant. Pathology samples acquisition guidelines and submission process will be outlined in the study Laboratory Manual to be provided by the vendors.

9.1.4 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), 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L), PROMIS Physical Function - Short Form 8c (PROMIS PF 8c) and the Patient Global Impression of Severity (PGIS).

The NSCLC-SAQ, FACT-L, EQ-5D-3L, PROMIS PF 8c and PGIS will be administered 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.

Section 2 provides information regarding the timing of patient-reported outcomes assessments during the study period. The baseline for outcome assessments must be performed prior to neo adjuvant C1D1 treatment. Additional information about the timing of each assessment is described below.

9.1.4.1 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 patients 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 (2 of the 9 items are not scored, and will not be administered) from the LCS will be used to calculate the FACT-Lung Cancer Subscale (FACT-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 Schedule of Assessment tables in Section 2.

9.1.4.2 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.[29] 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 unresectable NSCLC patients.

The NSCLC-SAQ will be administered per Schedule of Assessment tables in Section 2.

9.1.4.3 EQ-5D-3L

The EQ-5D-3L[30,31]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 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health 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 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, as described by the EQ-5D-3L. Altogether, the instrument describes $3^5 = 243$ health states.

Empirically-derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. 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-3L includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. The EQ-5D-3L uses a recall period of "today."

The EQ-5D-3L will be administered per Schedule of Assessment tables in Section 2.

9.1.4.4 PROMIS Physical Function

Physical function has been identified as a key domain for assessing symptom-related impacts and health-related quality of life (HRQoL) in patients with cancer in clinical trials. Physical function, along with symptoms of specific tumor types and symptomatic adverse events, can provide important data to support the safety and efficacy of a cancer treatment. The Patient-Reported Outcome Measurement Information System (PROMIS) is a set of self-report measurement tools that was developed by the US National Institutes for Health (NIH). PROMIS contains an item-bank of physical function items that assess a range of physical abilities. The PROMIS Physical Function Short Form 8c (PROMIS PF 8c) contains a subset of 8 items selected from the PROMIS Physical Function item bank, which were determined to be relevant to cancer patients. Each items assesses the difficulty a respondent has in performing different activities using a 5 level verbal rating scale. The PROMIS PF 8c uses a recall period of the past 7 days.

The PROMIS PF 8c will be administered per Schedule of Assessment tables in Section 2.

9.1.4.5 Patient Global Impression of Severity (PGIS)

Patient global impression of severity (PGIS) will be included as additional exploratory endpoint. The PGIS 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 PGIS will be used as anchor measures for use in assessing the psychometric measurement properties and the threshold for meaningful change for the NSCLC-SAQ.

The PGIS will be administered per Schedule of Assessment tables in Section 2.

9.2 Adverse Events

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

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

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

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.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 100 days after last dose of study treatment at the timepoints specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Refer to the Nivolumab IB for the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. For reference safety information on chemotherapy regimens, refer to the drug product labels. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

The collection of nonserious AEs (with the exception of nonserious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment.

All SAEs, and all AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

All SAEs must be collected that occur during the pre-screening/screening period, during treatment, within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- All SAEs, and all AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

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

All SAEs must be collected that occur during the screening period and treatment period and 100 days after the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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

9.2.2 Method of Detecting AEs and SAEs

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

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 9.2) and AEs (SAEs and nonserious 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, or until the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled out. Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 6 months or longer as per the local regulation and approved product label after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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 at the time of study intervention exposure, including at least 7 months after the study intervention administration, should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 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 DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.2.9 Management Algorithms for Immuno-Oncology Agents

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

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

The above algorithms are found in the nivolumab Investigator Brochure, as well as in Appendix 6.

9.3 Overdose

For this study, 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 the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Section 2 Schedule of Activities.

9.4.2 Vital signs

Refer to Section 2 Schedule of Activities.

9.4.3 ECG

Refer to Section 2 Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. A clinical safety laboratory assessment is required within 72 hours before each study drug treatment.

Table 9.4.4-1: Clinical 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 - screening only Sodium Potassium Chloride Calcium or ionized calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Serology	
Hepatitis B/C, (HBV sAG or HBV DNA, and HCV antibody or HCV RNA) - screening only HIV testing where locally mandated.	
Pregnancy test (WOCBP only minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening only as required to confirm menopause in women < age 55)	

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

Samples for PK and immunogenicity assessments will be collected for all participants in the treatment arm receiving nivolumab or nivolumab placebo (± chemotherapy). All time points are relative to the start of 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 immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

A detailed schedule of PK and immunogenicity evaluation is provided in Table 9.5-1. PK samples will be analyzed for nivolumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies and neutralizing antibodies by a validated method. Only samples from participants in the nivolumab treatment arm will be analyzed. Serum samples may be analyzed by an exploratory method that measures nivolumab for technology exploration purposes, exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg. insufficient volume for complete immunogenicity assessment or to follow upon suspected immunogenicity related AE).

Table 9.5-1: Pharmacokinetic and ADA Sampling Schedule

Study Day of Sample Collection[a]	Event	Time Relative to nivolumab/placebo dose	Nivolumab PK Sample [b]	Nivolumab ADA Sample[b]
Neoadjuvant treatment (1 Cycle = 3 weeks)				
Cycle 1 Day 1	Predose[c]	0:00	X	X
	End of infusion[d]	0:30	X	
Cycle 2 Day 1	Predose[c]	0:00	X	X
Cycle 3 Day 1	Predose[c]	0:00	X	X
Adjuvant treatment (1 Cycle = 4 weeks)				
Cycle 1 Day 1	Predose[c]	0:00	X	X
	End of infusion[d]	0:30	X	
Cycle 2 Day 1	Predose[c]	0:00	X	X
Cycle 3 Day 1	Predose[c]	0:00	X	X
Cycle 7 Day 1	Predose[c]	0:00	X	X
Cycle 11 Day 1	Predose[c]	0:00	X	X

[a] Part A1 indicates 4 cycles of neoadjuvant treatment of nivolumab/nivolumab placebo + chemotherapy prior to surgery. Part A2 indicates adjuvant treatment of nivolumab/nivolumab placebo monotherapy post surgery.

[b] If a subject discontinues nivolumab/nivolumab placebo treatment during the sampling period, PK and ADA samples should be only collected for the next 1 time point according to PK table.

[c] Predose samples should be collected just before the administration of nivolumab/nivolumab placebo (preferably within 30 minutes). 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.

[d] EOI: End of Infusion. This sample should be taken immediately prior to stopping nivolumab/nivolumab placebo drug infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered.

9.6 Pharmacodynamics

See Section 9.8.

9.7 Pharmacogenomics

See Section 9.8.

9.8 Biomarkers

9.8.1 Tumor Tissue and Blood Tissue Collection

Schedule for biomarker collection is found in Table 9.8.1-1.

Table 9.8.1-1: Biomarker Sample Schedule for All Participants

Study Day of Sample Collection	Tumor Archival or fresh biopsy in FFPE	Plasma for ctDNA[a, b]	Whole Blood DNA[a]	Serum (Soluble Factors)[a]	Whole Blood GEP[a, c]	Myeloid Derived Suppressor cells (MDSCs)[a, c]	PBMC[a, d]	SARS-CoV-2 Serology[c]
Diagnostic Biopsy	X							
Screening								X
Approximately 4 weeks after confirmed or suspected SARS-CoV-2 infection[e]								X
6 months after C1D1								X
Neoadjuvant treatment (1 cycle = 3 weeks)								
C1D1		X	X	X	X	X	X	
C4D21 or End of the last Neoadjuvant Treatment cycle		X		X	X	X	X	
Surgery prior to adjuvant treatment								
Surgery/Resection[f]	X	X[i]						
Adjuvant treatment during Year 1 (1 cycle = 4 weeks)								
Cycle 1 Day 1		X		X	X	X	X	
Cycle 2 Day 1		X		X	X	X	X	
Cycle 3 Day 1		X		X	X	X	X	
Every Cycle Day 1, starting at		X						

Table 9.8.1-1: Biomarker Sample Schedule for All Participants

Study Day of Sample Collection	Tumor Archival or fresh biopsy in FFPE	Plasma for ctDNA[a, b]	Whole Blood DNA[a]	Serum (Soluble Factors)[a]	Whole Blood GEP[a, c]	Myeloid Derived Suppressor cells (MDSCs)[a, c]	PBMC[a, d]	SARS-CoV-2 Serology[c]
Cycle 4 Day 1 until Cycle 13								
Disease surveillance								
Recurrence or Disease Progression[h]	X[g]	X[i]		X	X	X	X	

a Prior to dosing (when applicable)

b Plasma ctDNA samples should only be collected during Years 2 through 5 at the time of recurrence or progression. If a participant does not have surgery and/or adjuvant therapy, plasma ctDNA samples should not be collected during adjuvant or disease surveillance/Follow-up. If a participant discontinues adjuvant treatment early, plasma ctDNA samples should not be collected during disease surveillance/Follow-up.

c SARS-Cov-2 serology, Whole Blood GEP and MDSCs are not collected in China.

d PBMCs are not collected in Australia and China.

e A sample is collected approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG).

f Assessment of pathological response and additional biomarker analysis. Please refer to CA20977T laboratory manual.

g At the time of disease recurrence or progression, excised tumor tissue submission (FFPE block [preferred] or 10 to 15 unstained slides), obtained from core biopsy, excisional biopsy, or surgical specimen is optional but strongly encouraged. Fine needle aspirates of draining lymph node are not acceptable. Core needle biopsies obtained by EBUS are acceptable. If a sample is collected, see CA20977T Laboratory Manual for tissue requirements.

h Samples collected upon recurrence or progression of the disease should be collected prior to subsequent therapy.

i ctDNA plasma collections at “Surgery/Resection” and “Recurrence or Disease Progression” should be obtained prior to surgery or tumor sample collection.

9.8.1.1 Diagnostic/Baseline Biopsy

Tumor tissue submission prior to randomization is mandatory. If a recent/archived (within 3 months from randomization) biopsy sample is not available at screening, then a fresh biopsy will be taken.

Sufficient tumor tissue obtained prior to randomization (FFPE block or 5 to 10 unstained slides, obtained from core biopsy, excisional biopsy or surgical specimen) is acceptable. For participants for whom a fresh biopsy is not feasible, archival tumor material obtained within 3 months prior to randomization must be made available. Fine needle aspirate of draining lymph node is not acceptable. Core needle biopsies obtained by EBUS are acceptable.

9.8.1.2 Whole Exome Sequencing of Tissue and Whole Blood DNA

After the participant has enrolled in the study, the participant will undergo surgery and surgical tumor sample(s) will be submitted for GCLP approved whole exome sequencing. An assessment of biopsy quality by a pathologist/cytopathologist is encouraged at the time of procedure. Please refer to the lab manual for specific tumor collection instructions. Assessment of deep whole exome next-generation sequencing, that targets entire coding region (exome) within genome will be performed to allow evaluation of specific mutations and aggregate. The tissue signature mutations will define residual disease progression by following defined gene variants in the whole blood. Identification of target mutations in the tissue requires paired blood (whole blood DNA sample) for germline variation subtraction, exomes from both tumor and blood are sequenced and are compared to one another for germline variant correction.

9.8.1.3 Tissue Biopsy at Disease Progression or Recurrence

Upon disease progression/recurrence, excised tumor tissue submission (FFPE block [preferred] or 10 to 15 unstained slides), obtained from core biopsy, excisional biopsy, or surgical specimen is optional but strongly encouraged upon disease progression/recurrence and prior to subsequent systemic treatment. Fine needle aspirates of draining lymph node are not acceptable. Core needle biopsies obtained by EBUS are acceptable. Tissue upon disease progression/recurrence should be performed prior to subsequent systemic treatment. Biopsy samples collected at the time of disease progression or recurrence is to evaluate changes in exploratory biomarkers, which may provide critical insight into the tumor microenvironment (TME) at the time of acquired resistance. The procedure may be performed if deemed an acceptable clinical risk as judged by the investigator or in consultation with the radiology staff. Such analyses may inform future combination strategies designed to prevent/delay acquired resistance to nivolumab.

9.8.1.4 Circulating tumor DNA (ctDNA)

ctDNA analysis will be used to identify single nucleotide variants for disease monitoring or mimimal residual disease. Additional batched analyses of ctDNA isolated from on treatment patients can be utilized to perform non-invasive phylogenetic analyses of tumor evolution under the selective pressure of systemic treatment in a research setting. The longitudinal analyses of MRD+ status patient samples potentially allows tracking of adjuvant chemotherapy/IO resistance and identifies patients destined to experience recurrence of their lung cancer. This biomarker provides phylogenetic ctDNA profiling of subclonal nature of lung cancer relapse and metastases, providing a new approach for ctDNA driven therapeutic studies.

Timepoints for ctDNA plasma collection pre and post treatment are in Table 9.8.1-1.

9.8.1.5 Serum Soluble Factors

Serum will be obtained from all participants prior to first dose of study drug and during the study. To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of study treatment, panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be investigated by ELISA, seromics, and/or other relevant multiplex-based protein assay methods. Circulating proteins of interest may include, but

are not limited to, factors induced by IFNγ signaling (eg, T cell chemoattractants CXCL9; CXCL10) antibodies to tumor-associated antigens, and soluble PD-L1 (sPD-L1).

9.8.1.6 Tissue and Whole Blood Gene Expression

Resected tumor specimen and peripheral blood will be collected (prior to- and during treatment) to evaluate baseline and changes from baseline in gene expression patterns. Signaling pathways, both immune-related and non-immune related, may be explored for association with response to treatment. Gene expression data will be generated from tissue and blood using RNAseq or similar methodology.

Note: Whole blood GEP will not be collected in countries where not logistically feasible.

9.8.1.7 Peripheral blood mononuclear cells (PBMCs)

To assess the immunomodulatory properties of nivolumab over the course of treatment, peripheral blood samples will be collected from all participants according to the schedule provided in Table 9.8.1-1 and will be used to prepare viable PBMCs. Cytometric analyses (such as, but not limited to flow, chip- and mass-spec-based) may be completed using these samples to quantify increases or decreases from baseline in various immune cell populations, including but not limited to activated (HLA-DR+), memory (CD45RO+), and regulatory (FoxP3+) T cells. Baseline levels and changes from baseline levels in candidate biomarkers, assessed by cytometry analyses will be evaluated for association with efficacy and/or safety. Additional analyses of PBMCs may include functional assessment using methods such as, but not limited to, tetramer analysis and/or EliSpot analysis, potentially using peptides derived from neoantigen prediction studies from whole exome sequencing in tumor samples.

Note: PBMCs will not be collected in countries where not logistically feasible.

9.8.1.8 Myeloid Derived Suppressor Cells (MDSCs)

Myeloid derived suppressor cells are an immune cell population capable of suppressing T cell activation and proliferation. Low pre-treatment MDSC levels in peripheral blood may be associated with better overall survival in NSCLC patients treated with the immunotherapeutic agent MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic changes or associations with outcome.

Note: MDSCs will not be collected in countries where not logistically feasible.

9.8.1.9 Other Assessments

Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or IgG) to explore potential association with safety, efficacy, and/or immune biomarkers.

9.8.2 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites: Additional research participation is required for all investigational sites in the U.S.

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

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

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

Residual whole blood, serum, plasma, and tumor biopsy/surgical collections (see Table 9.8.2-1) will be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

All samples from screened participants will be archived at the BMS Biorepository or an independent, BMS-approved storage vendor.

Table 9.8.2-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK/Immunogenicity	All
Tumor Biopsy	All
Surgical tissue	All
Blood samples for biomarkers	All

9.8.3 Immunogenicity Assessments

Immunogenicity samples will be analyzed for anti-nivolumab antibodies and neutralizing antibodies by a validated method. Only samples from participants in the nivolumab treatment arm will be analyzed. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes, exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg. insufficient volume for complete immunogenicity assessment or to follow upon suspected immunogenicity related AE). Further details of blood collection and processing will be provided to the site in the procedure manual.

A detailed schedule of immunogenicity evaluation is provided in Table 9.5-1.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Healthcare resource utilization data will be collected for all randomized participants using an internal CRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including the number of days spent in various wards and discharge diagnosis, and non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The healthcare 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 event-free survival (EFS) in nivolumab plus chemotherapy (Arm A) and placebo plus chemotherapy (Arm B). Initially, an alpha of 0.05 will be allocated to the EFS comparison of Arm A vs Arm B, and if that comparison is statistically significant, the full alpha will be reallocated to the overall survival comparison of Arm A vs Arm B.

10.1.1 Sample Size Justification for EFS

In this study, the sample size is calculated to compare EFS between Arm A and Arm B under a two-side 0.05 type I error with 90% power consideration. The number of events was estimated assuming an exponential distribution for EFS in each arm.

Approximately 452 subjects will be randomized to the two treatment groups in a 1:1 ratio. Approximately 231 EFS events observed among the above described population provides 90% power to detect a hazard ratio (HR) of 0.65 with a type 1 error of 0.05 (two-sided). The HR of 0.65 corresponds to a 54% increase in the median EFS, assuming a median EFS of 21 months for Arm B and 32.3 for Arm A. The interim analyses is scheduled to take place after approximately 185 events (80% of the total number of events), which corresponds to 32 months after the first subject is randomized. The stopping boundaries at the interim and final analyses will be based on the actual number of EFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis is performed exactly at 185 events, the study

could be stopped by the DMC for EFS superiority if the p-value is ≤ 0.025. The nominal significance level for the final look of EFS after 231 events would then be 0.043.

Assuming the accrual rate (number of randomized subjects per month: 20), it will approximately take 38 months (23 months for accrual and 15 months for follow-up) from the randomization of the first subject to observe the required number of events among subjects randomized for final EFS analysis.

Table 10.1.1-1 summarizes of the key parameters of the sample size justification for EFS Analyses.

Table 10.1.1-1: Sample Size Justification for EFS Analyses

Primary Endpoint	EFS
Primary analysis Comparison population	Arm A and Arm B
Power (interim analysis /final analysis)	90% (75% / 15%)
Alpha	0.05
Hypothesized Median nivolumab + chemotherapy (arm A) vs placebo + chemotherapy (arm B) (months)	32.3 vs 21
Hypothesized Hazard ratio	0.65
Accrual Duration (months)	23
Timing of interim analysis(IA) from randomization of first subject (months)	32
Timing of final analysis(FA) from randomization of first subject (months)	38
Sample size for Arms A and B	452
Expected number of events for EFS interim analysis 1 (80% events) EFS final analysis	 185 231

10.1.2 Power Calculation for OS

If the superiority of EFS per BICR assessment for the comparison between nivolumab plus chemotherapy (Arm A) and placebo plus chemotherapy (Arm B) is demonstrated at a two sided type I error rate 0.05, OS will be tested hierarchically (Section 10.3.2) .

Approximately 174 events, among the 452 subjects randomized to Arms A and B provides 80% power to detect a hazard ratio of 0.65 with a type I error of 0.05. The HR of 0.65 corresponds to a 54% increase in the median OS, assuming a median OS of 40 months for Arm B and 61.5 months for Arm A. One interim analysis are planned at the time of the EFS FA (where approximately 80% of the total number of events are projected to have occurred at 140 events). The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the first interim analysis is performed exactly at 140 events, a p-value ≤ 0.025 would result in a

statistically significant improvement in OS. The nominal significance level for the final look of OS after 174 events would then be 0.043.

Assuming an accrual rate of 20 participants per month, it will take approximately 46 months from the randomization of the first subject to observe the required number of events for the final OS analysis. The interim analysis will take place at the same time as the final EFS analysis, which is projected to be 38 months from the randomization of the first subject. Table 10.1.2-1 summarizes the key parameters of the power calculation for OS Analyses.

Table 10.1.2-1: Power Calculation for OS Analyses

Secondary Endpoint	OS
Primary analysis Comparison population	Arm A and Arm B
Power (interim analysis /final analysis)	80% (60% / 20%)
Alpha	0.05
Hypothesized Median nivolumab + chemotherapy (arm A) vs placebo + chemotherapy (arm B) (months)	61.5 vs 40
Hypothesized Hazard ratio	0.65
Accrual Duration (months)	23
Timing of interim analysis(IA) from randomization of first subject (months)	38
Timing of final analysis(FA) from randomization of first subject (months)	46
Sample size for Arms A and B	452
Expected number of events for OS interim analysis 1 (80% events) OS final analysis	 140 174

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled participants	All participants who sign informed consent and were registered into the IRT
Treated participants	All participants who received at least one dose of study medication in neoadjuvant or adjuvant setting. This is the primary dataset for drug exposure and safety analysis.
PK participants	All treated subjects with available serum time-concentration data
Randomized participants	All participants who were randomized to any treatment arm in the study. This population will be used for analyses of study conduct and study population. Analysis of demography, protocol

Population	Description
	deviations, baseline characteristics and efficacy will be performed for this population
Biomarker participants	All treated subjects with biomarker data available.
Patient-Reported Outcome participants	All treated subjects who have a valid baseline assessment and at least one post baseline assessment

10.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. For the stratified test, stratum may be combined if stratum size is too small. Additional details will be outlined in the SAP. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

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

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
Event-free Survival	EFS is defined as the length of time from randomization to any of the following events: progression of disease or worsening of disease precluding surgery, if surgery is attempted but gross resection is abandoned due to unresectable tumor or worsening of disease, progression or recurrence of disease after surgery, progression of disease for participants without surgery, or death due to any cause. Progression/recurrence will be assessed by BICR per RECIST 1.1. Participants who do not undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 progression or death. Participants who undergo surgery with incomplete resection (residual disease visible on imaging) will be considered to have an event at RECIST 1.1 progression or death. Participants who die without a reported progression/disease recurrence will be considered to have experienced an event on the date of their death. Participants who do not report progression/recurrence of disease 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 the date they were randomized. Participants who started any subsequent anti-cancer therapy outside of the protocol-specified adjuvant therapy without a prior reported progression/recurrence will be

Endpoint	Statistical Analysis Methods
	censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. There are two scheduled EFS analyses: one EFS interim analysis and one EFS final analysis. EFS primary hypothesis testing will be conducted between 2 randomized arms via a 2-sided, log rank test stratified by the stratification factor (ie, tumor histology, PD-L1 status and tumor stage). The alpha spending allocated to the testing is based on the number of events at the time of interim analyses based on Lan-DeMets alpha spending function. The hazard ratio and the two sided 95% confidence interval will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate. In addition, EFS rates at 6, 12, 18 and 24 months will be estimated using KM estimates on the EFS curve for each randomized arm provided a minimum follow-up is longer than the time point to generate the rate. Associated 2-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation). Sensitivity analysis on EFS will also be performed, and details will be included in statistical analysis plan.
Secondary	
Overall survival	If the comparison of primary endpoint EFS is statistically significant, OS will be tested hierarchically and the full alpha (0.05) will be recycled to the OS comparison. There will be one interim analysis and one final analysis scheduled for the OS comparison and the alpha spending allocated to the testing is based on the number of events at the time of the interim analysis based on the Lan-DeMets alpha spending function. Hazard ratios (HR) of OS and corresponding two-sided 95% confidence intervals (CI) will be estimated using a stratified Cox proportional hazard model, with treatment group as a single covariate. OS curves, OS medians with 95% CIs, and OS rates at 6, 12, 18, 24 and 36 months with 95% CIs will be estimated by treatment group using Kaplan Meier methodology if follow-up requirement is met. 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 subject was known to be alive. OS will be followed continuously while participants are on the study drug and every 3 months via in-person or phone contact after participants discontinue the study drug.

Endpoint	Statistical Analysis Methods
Pathologic Complete Response and Major Pathological Response	Pathological response will be summarized by category for each treatment group. MPR and pCR rate will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. The stratified by tumor histology, PD-L1 status and tumor stage odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. In addition, an estimate of the difference in MPR and pCR rates and corresponding 95% CI will be calculated using CMH methodology and adjusted by stratification factors.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.2 Safety Analyses

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 drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE will be individually characterized in the SAP.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.3 Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

PFS2 is defined as the time from randomization to the date of investigator-defined documented disease progression after next line of treatment or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. A participant who neither progresses after next line of treatment nor dies will be censored on the last known date alive. A participant who does not have any post baseline tumor assessments and who has not died will be censored on the date at which he/she was randomized.

Methodology for exploratory immunogenicity analyses is described in the statistical analysis plan.

10.3.4 Interim Analyses

One formal interim analysis for EFS is planned after approximately 185 events have been observed. This is projected to occur approximately 32 months after start of randomization. The formal comparisons of EFS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of events using Lan-DeMets α spending function with O'Brien and Fleming type of boundary. If the analysis were performed exactly at 185 events, the boundary for declaring superiority would be 0.025. An independent statistician external to BMS will perform the analyses.

If the study continues beyond this interim analyses, the nominal significance level for the final look after 231 EFS events would be 0.043. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol, final boundary will not be recalculated using updated information fraction at interim.

If the EFS comparison is statistically significant, one formal interim analysis for OS is planned at the time of the EFS FA (corresponding to approximately 80% of the total number of events). The formal comparisons of OS will allow for early stopping for superiority. The stopping boundary will depend on the actual number of events at the time of the interim analysis

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

11 REFERENCES

[1] Mountain, CA. Regional lymph node classification for lung cancer staging. Chest. 1997: 1718-23.

[2] Douillard JY, R. R. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncology. 2006;7: 719-27.

[3] Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol. 2010 Jan;5(1):29-33.

[4] Mountain, CA. Regional lymph node classification for lung cancer staging. Chest. 1997: 1718-23.

[5] NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010 Apr 10;375(9722):1267-77.

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. A Cancer J Clin. 2015; 65(1):5-29.

[7] Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med, 2004, 351-60.

[8] Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group and Northern Central Cancer Treatment Study Groups. Journal of Clinical Oncology. 2008;26: 5043-51.

[9] Winton T, L. R. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352: 2589-97.

[10] Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol. 2006 Sep;1(7):611-21.

[11] Provencio-Pulla M, Nadal-Alforja E, Cobo M. Neoadjuvant chemo/immunotherapy for the treatment of stages IIIA resectable non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study—NADIM study-SLCG. 2018. Journal of Clinical Oncology 36,15:8521-8521.

[12] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6:715-27.

[13] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

[14] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991-8.

[15] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2004;23:515-48.

[16] Freeman FJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunohibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000; 192(7): 1027-34.

[17] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol. 2007;8:237-45.

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

[19] van der Most RG, Currie AJ, Mahendran S, et al. Tumor eradication after cyclophosphamide depends on concurrent depletion of regulatory T cells: A role for cycling TNFR2-expressing effector-suppressor T cells in limiting effective chemotherapy. Cancer Immunol Immunother. 2008;58:1219–28.

[20] Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity. 2013;39:74–88.

[21] Harris SJ, Brown J, Lopez J, and Yap TA. Immuno-oncology combinations: raising the tail of the survival curve Cancer Biol Med. 2016 Jun; 13(2): 171–193.

[22] Amin MB, Greene FL, Edge S. American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Edition 8, Springer. 2018.

[23] PARAPLATIN (carboplatin aqueous solution) INJECTION. Updated July 2010. Bristol-Myers Squibb Company, Princeton, NJ.

[24] Platinol (cisplatin for injection). Prescribing information. Revised May 2010. Bristol-Myers Squibb Company, Princeton, NJ.

[25] Docetaxel (Taxotere□) Prescribing Information, 2011.

[26] Paclitaxel Aurobindo 6 mg/ml Concentrate for solution for infusion. Summary of Product Characteristics. Puren Pharma.

[27] Taxol (paclitaxel) Injection. Corden Pharma Latina. January 2011.

[28] ALIMTA® (pemetrexed for injection), for Intravenous Use. Update September 2013. Lilly, USA, Inc. Indianapolis, IN.

[29] Kelly P.McCarrier, PhD, MPH; Thomas M.Atkinson, PhD; Kendra P.A. DeBusk, PhD; Astra M.Liepa, PharmD; Michael Scanlon, MA; Stephen Joel Coons, PhD on behalf of the Patien Reported Outcome Consortium,Non–Small Cell Lung Cancer Working Group. Qualitative Development and Content Validity of the Non–small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), A Patient-reported Outcome Instrument. Clinical Therapeutics. 38(4), 2016; 794-810.

[30] EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 16, 199–208 (1990).

[31] Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	Additional Research
AST	aspartate aminotransferase
BICR	Blinded independent central review
BID, bid	bis in die, twice daily
BIPR	Blinded independent pathological review
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^-$	chloride
cm	centimeter
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form, paper or electronic
cRR	clinical response rate
CT	computed tomography
ctDNA	circulating tumor deoxyribonucleic acid
dL	deciliter
DLco	carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EBUS	endobronchial ultrasound
ECG	electrocardiogram

Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	event-free survival
eg	exempli gratia (for example)
EQ-5D-3L	European Quality of life 5 dimensions 3 level
EU	European Union
EWB	emotional well-being
FACT-G	FACT-General
FACT-L	Functional Assessment of Cancer Therapy – Lung
FACT-LCS	FACT-Lung Cancer Subscale
FDA	Food and Drug Administration
FEV1	forced expiratory volume in the first second of expiration
FFPE	formalin-fixed paraffin-embedded
FRC	functional residual capacity
FSH	follicle stimulating hormone
FVC	forced vital capacity
FWB	functional well-being
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GWAS	genome-wide association study
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HRQoL	health-related quality of life
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)

Term	Definition
IEC	Independent Ethics Committee
IHC	Immunohistochemical
IMP	investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LAM	lactation amenorrhea method
LCS	Lung Cancer Subscale
LDH	lactate dehydrogenase
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MPR	major pathological response
MLND	mediastinal lymph node dissection
MRI	magnetic resonance imaging
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NSCLC	non-small cell lung carcinoma
NSCLC-SAQ	non-small cell lung cancer symptom assessment questionnaire
NIMP	non-investigational medicinal products
OS	overall survival

Term	Definition
PBMC	peripheral blood mononuclear cells
pCR	Pathologic complete response
PET	positron emission tomography
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PPK	Population pharmacokinetic
PO	per os (by mouth route of administration)
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcome Measurement Information System
PROMIS PF 8c	PROMIS Physical Function Short Form 8c
PWB	physical well-being
QOL	quality of life
R&D	Research and Development
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SOC	Standard of care
SOP	Standard Operating Procedures
t	temperature
TAO	Trial Access Online, the BMS implementation of an EDC capability
TLC	total lung capacity
TME	tumor microenvironment
VAS	visual analog scale
WHO	World Health Organization
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 GuidelinesGood Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

All potential serious breaches must be reported to 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 subjects 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 subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance

understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

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

The confidentiality of records that could identify subjects 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.

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, 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.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care 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 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.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

SCIENTIFIC PUBLICATIONS

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

Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> 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 <u>NOT</u> 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

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

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 • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 7 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

• Progestogen-only hormonal contraception must begin at least 7 days prior to initiation of study therapy.
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 • Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study 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.
- 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.
- 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.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 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

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

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

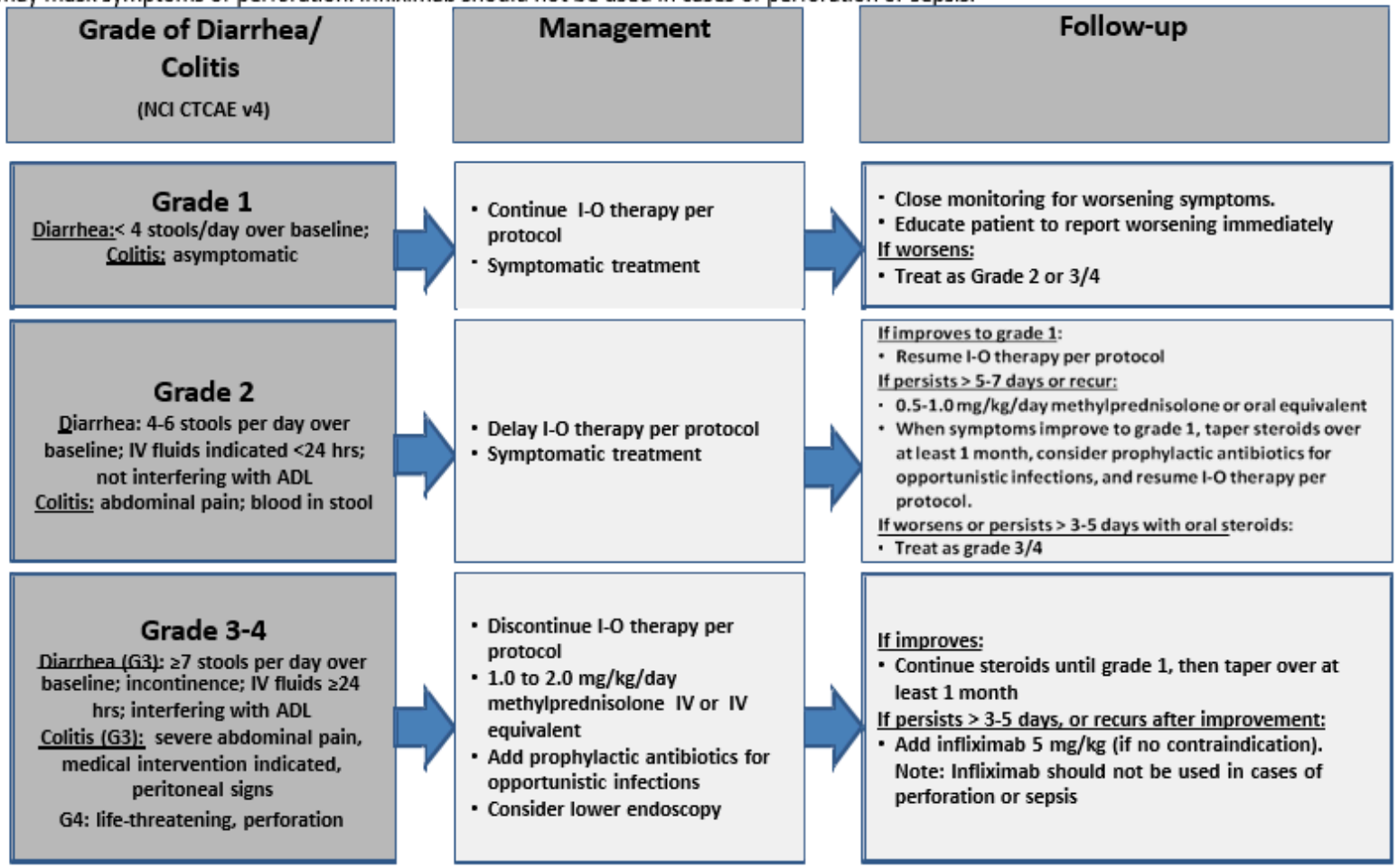
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

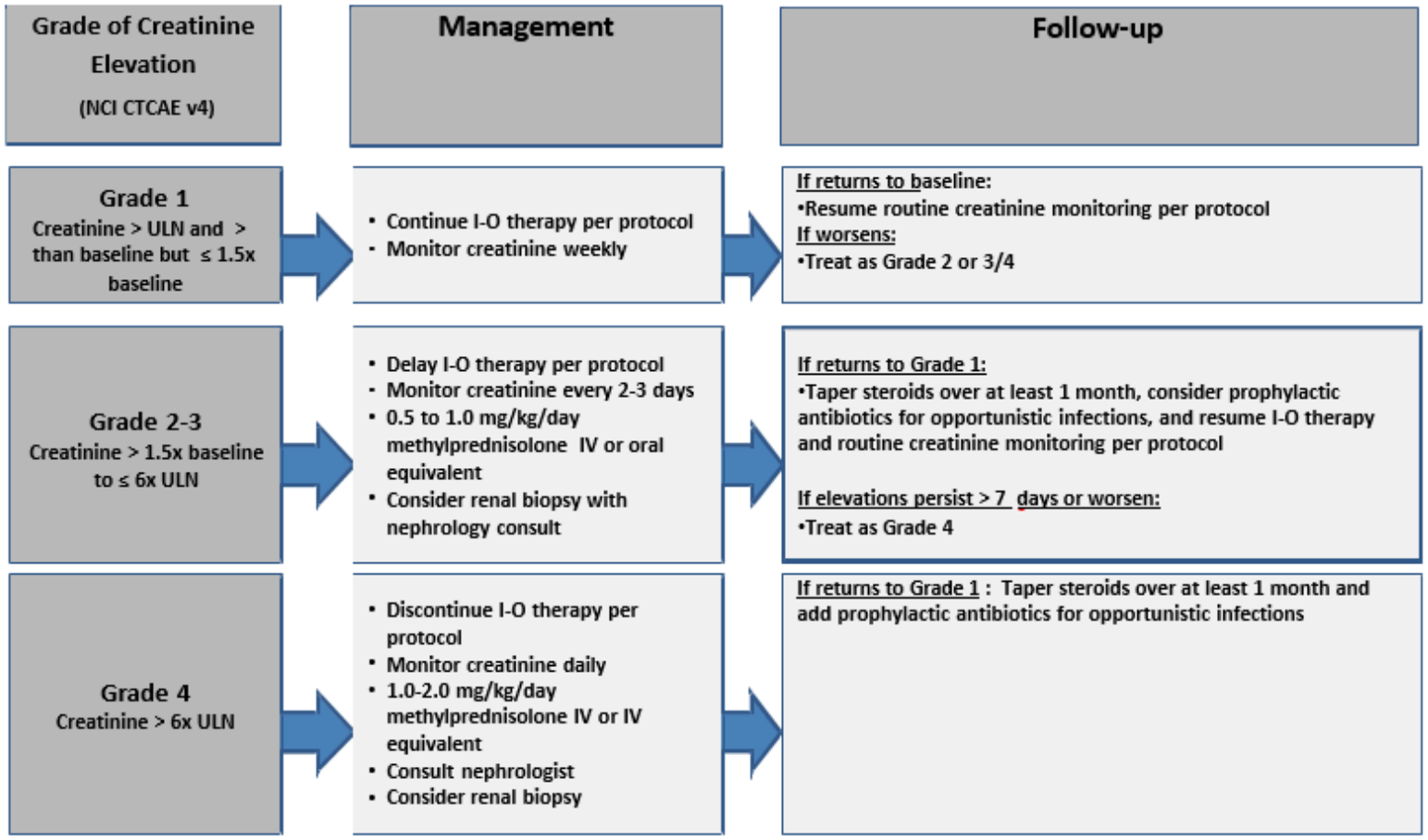


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

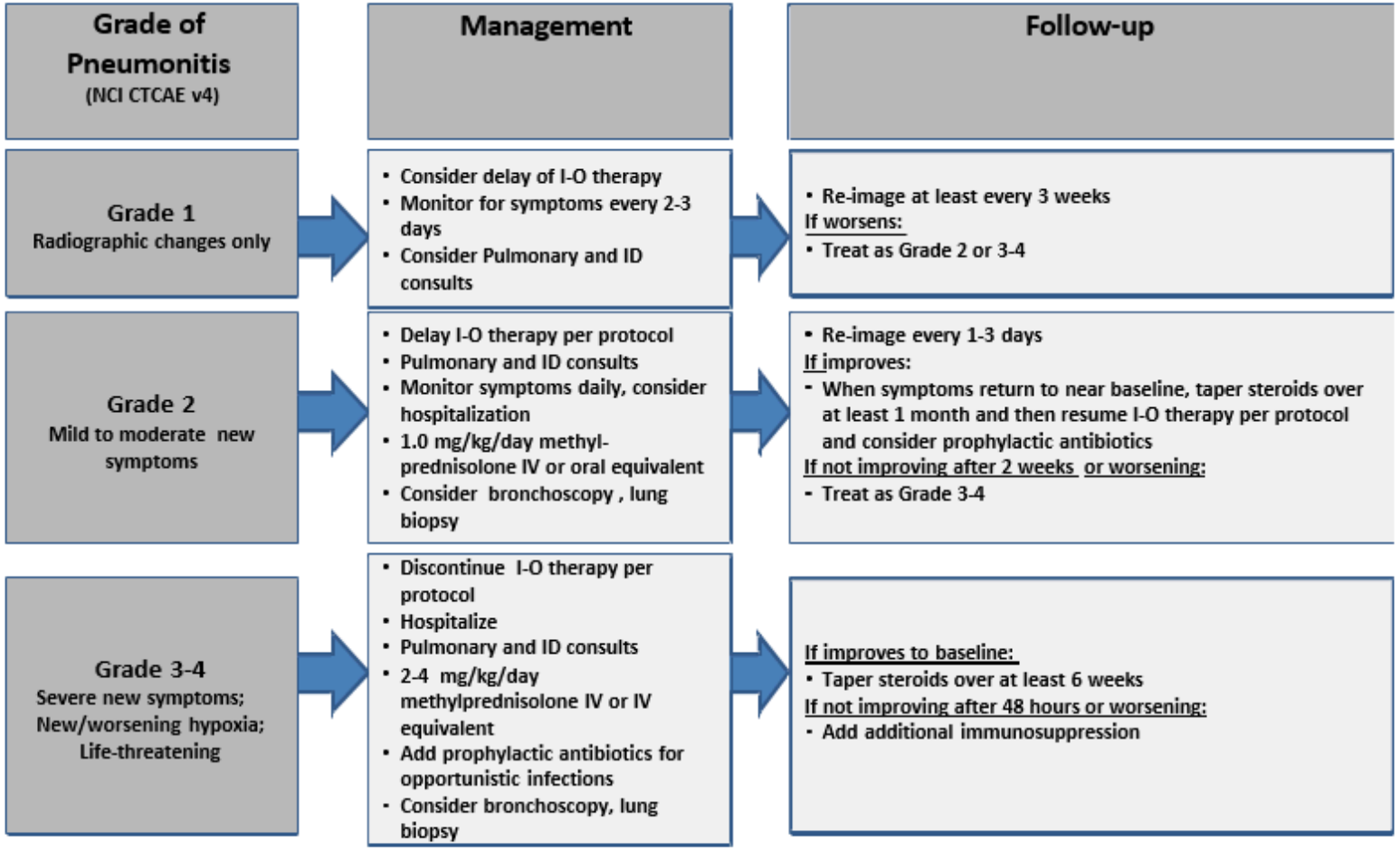


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

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

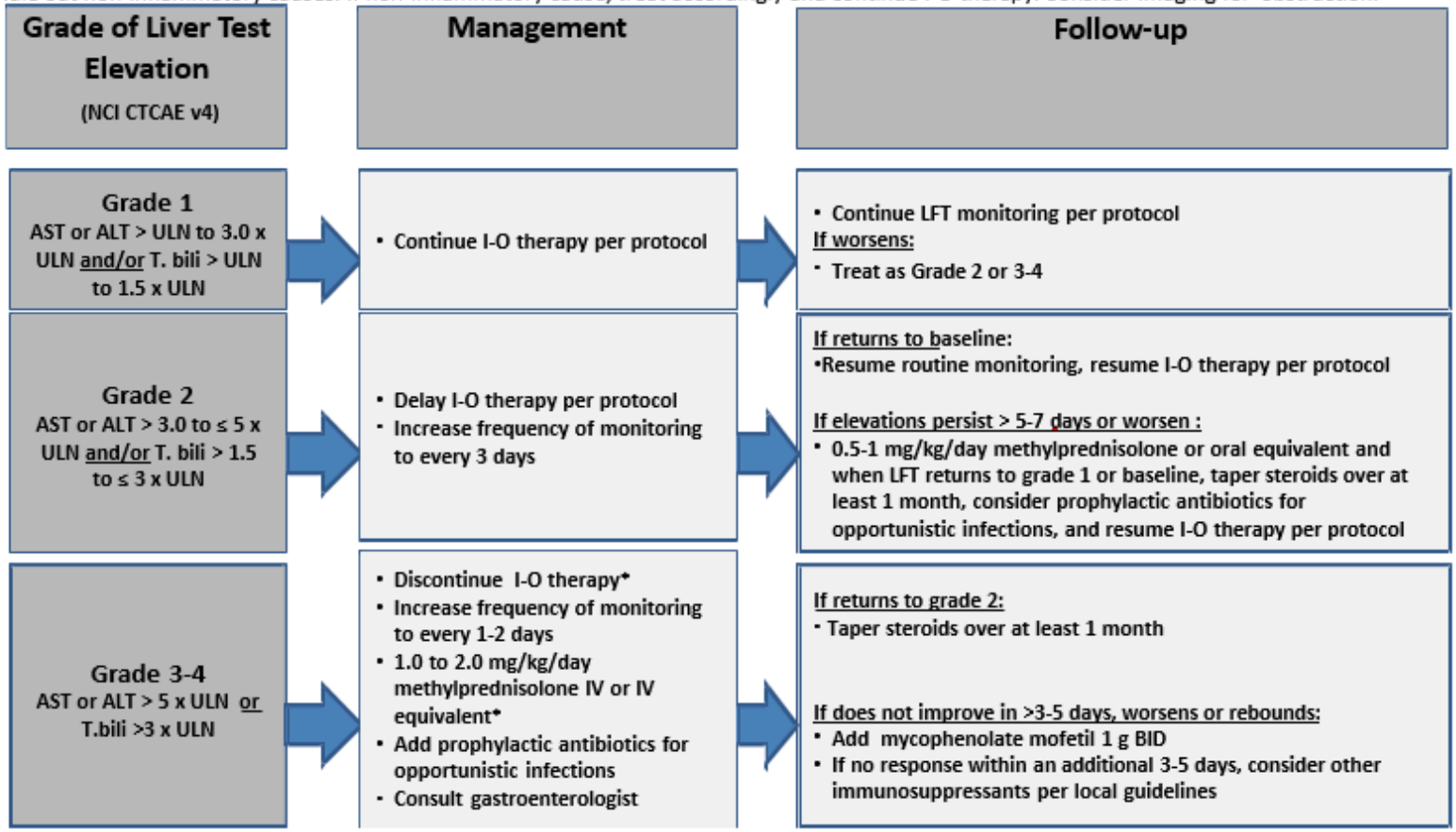


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

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



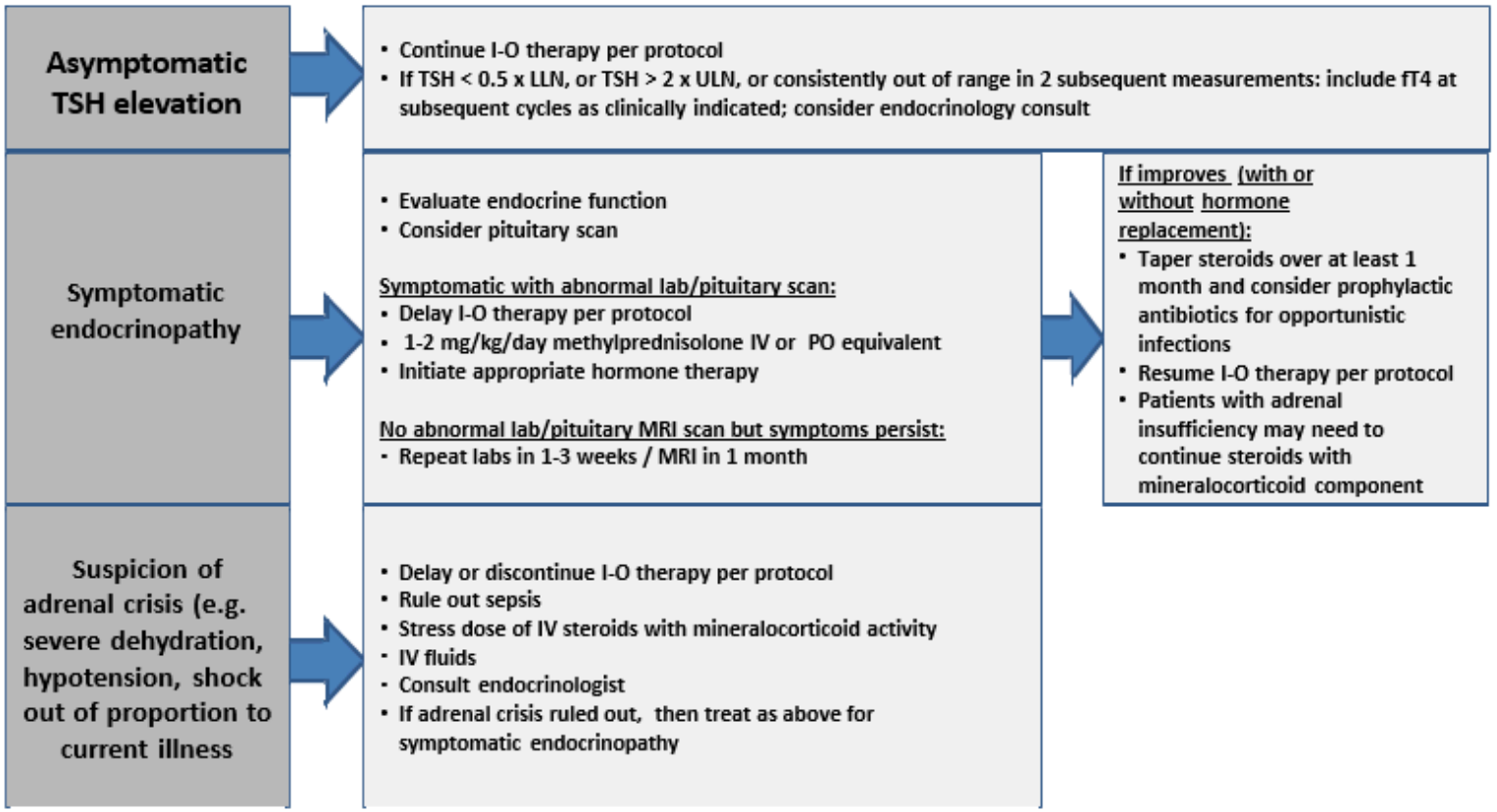
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

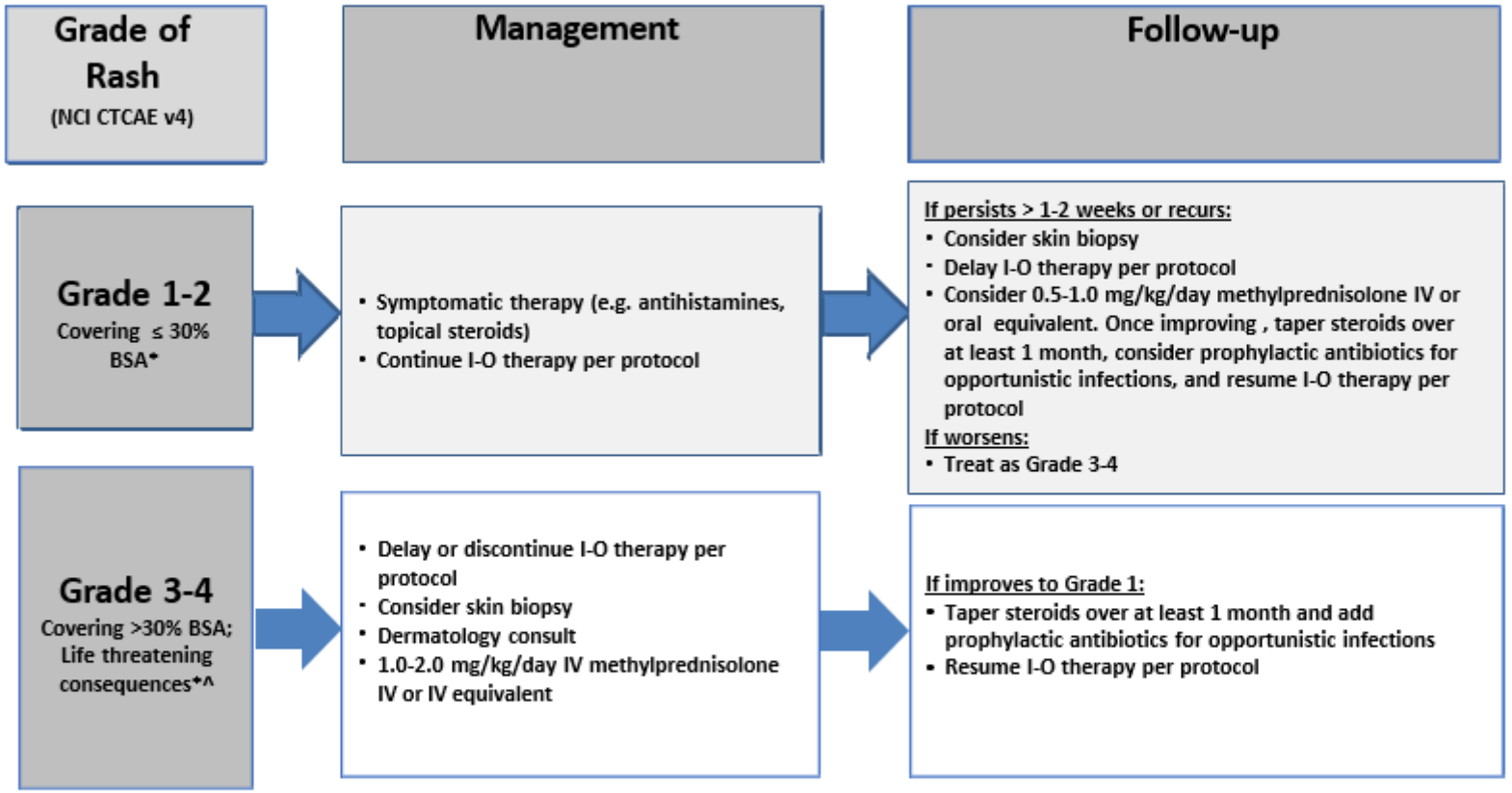


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

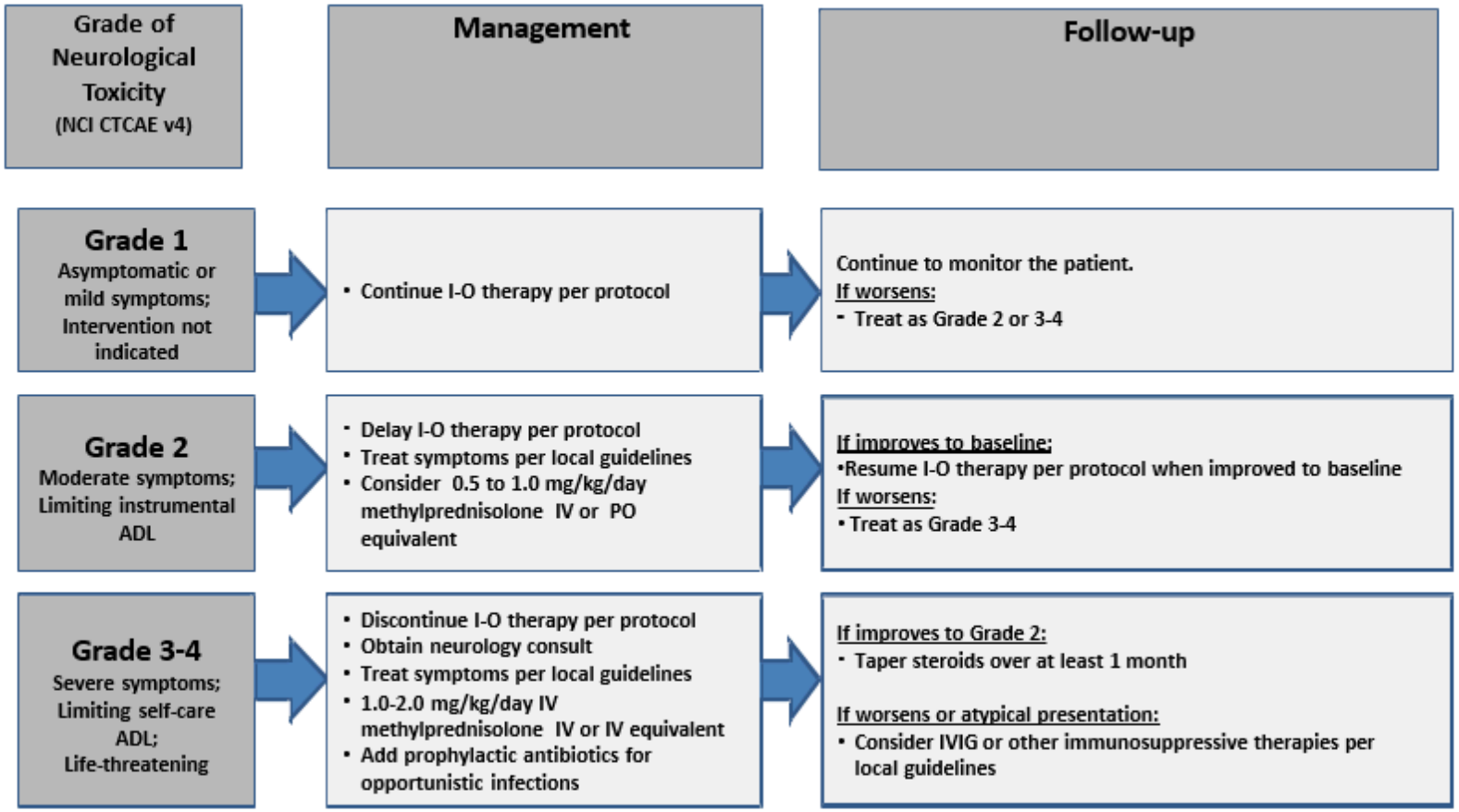
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2019

Neurological Adverse Event Management Algorithm

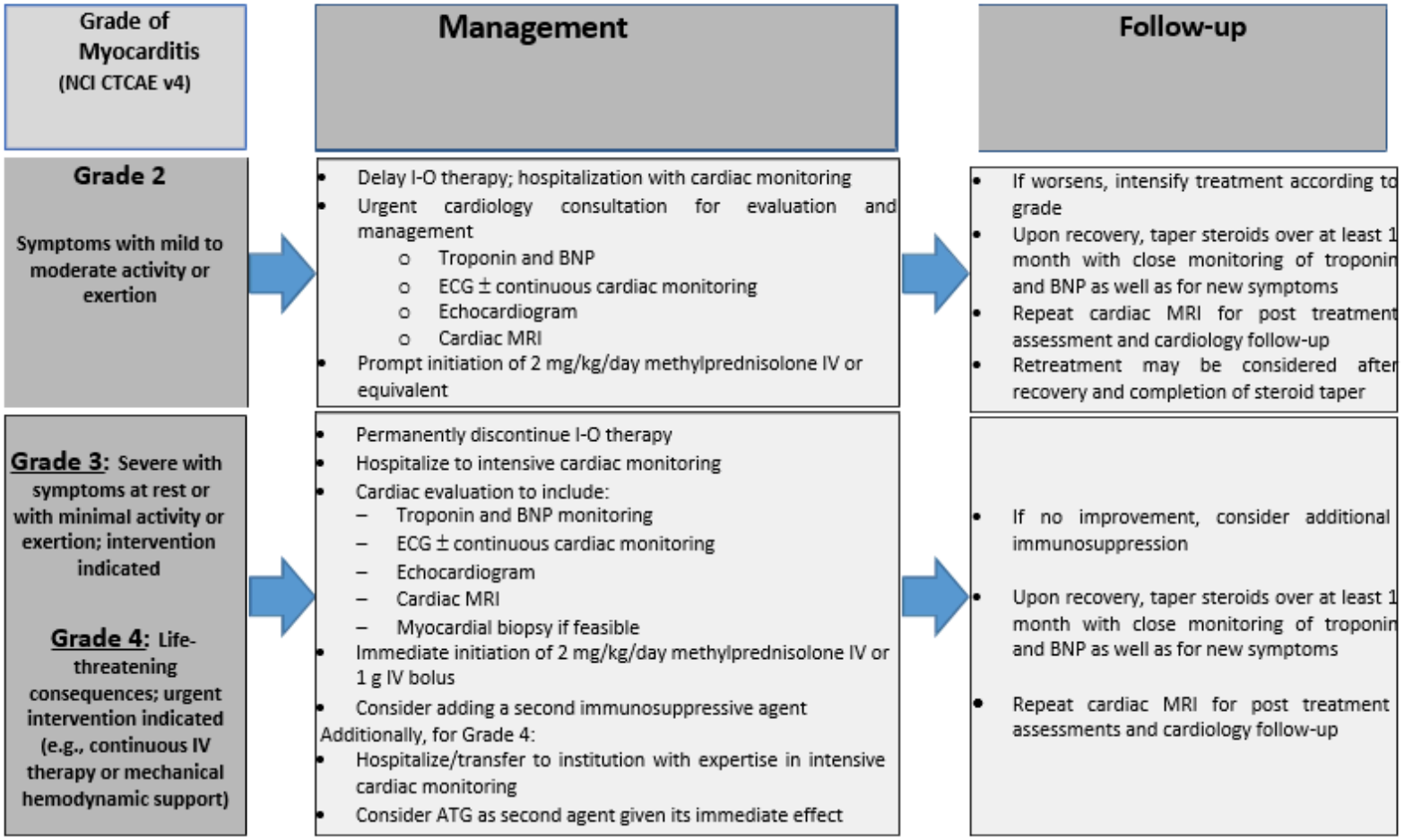
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

27-Jun-2019

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

27-Jun-2019

APPENDIX 7 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS FOR NEOADJUVANT LUNG STUDY

HIGH LEVEL SUMMARY OF THE MODIFICATIONS

- Removal of fluid (ascites, pleural and pericardial effusions) from response assessment as non-target or new lesion due to potential unconfirmed etiology and volume changes resulting from interventional procedures unrelated to treatment response (thoracentesis),
- Best Overall Response of CR or PR does not require confirmation.

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 in the Neoadjuvant (Pre-surgery) phase.

For patients who undergo surgery, best overall response is assessed from start of the study treatment to tumor assessment prior to definitive surgery

For patients not undergoing definitive surgery, the best response is assessed from the start of study treatment until the first scheduled tumor assessment per protocol.

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. Assessments of partial response and complete response do not require confirmation.

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

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
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 does not require confirmation. 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.

Best overall response is defined as:

- For patients undergoing definitive surgery: the best response is recorded from the start of study treatment until the last tumor assessment performed prior to definitive surgery.
- For patients not undergoing definitive surgery: the best response is recorded from the start of study treatment until the first scheduled tumor assessment per protocol.

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).

2.3.4 Confirmation Scans

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

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 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Amendment 03, 20-Apr-2021

The overall rationale for the amendment is to reduce the number of slides required at screening and change the requirement for biopsy at disease progression/recurrence from mandatory to optional in order to address potential barriers to enrollment, reduce burden on participants, and reduce trial complexity. In addition, the definition of Event-Free Survival was aligned throughout protocol sections, imaging requirements were clarified, and response evaluation criteria was clarified. Serology samples for SARS-CoV-2 were added. AE collection was updated to include collection of SARS-CoV-2-related adverse events. These changes apply to all patients.

Summary of Key Changes for Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline	• Documentation of COVID-19 vaccine or infection history added	• Added to specify that collection of COVID-19 vaccination status will be collected as part of participants medical history
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline; Section 9.8.1.1, Diagnostic/Baseline Biopsy	• Required tissue amount updated to 5-10 slides • Serology samples for SARS-CoV-2	• The number of tissue slides reduced from 15 to 5-10, to address potential enrollment barriers • Serum will be collected for potential future anti-SARS-CoV-2 based analysis
Section 2, Schedule of Activities, Table 2-2: Neoadjuvant and Pre-Surgery Procedures and Assessments; Table 2-3: Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments; Table 2-4: Long-term Follow up Assessment; Table 9.8.1-1: Biomarker Sample Schedule for All Participants; Section 9.8.1.3, Tissue Biopsy at Disease Progression or Recurrence	• Reduction in number of slides required at enrollment from 15 to 5-10. • Biopsy upon disease progression/recurrence changed from mandatory to optional	• To reduce burden on participants and reduce trial complexity
Section 2, Schedule of Activities; Table 2-1 Screening Procedural Outline; Table 2-2:	• Updated note added to AE collection related	• SARS-CoV-2 AEs/SAEs will be collected

Summary of Key Changes for Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Neoadjuvant and Pre-Surgery Procedures and Assessments; Table 2-3: Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments; Table 2-4: Long-term Follow up Assessment;	to SARS-CoV-2 infection	
Section 2, Schedule of Activities, Table 2-4: Long-term Follow-up Assessments	• Clarification of body imaging requirements to include participants who do not undergo surgery	• To provide language clarity for schedule of activities
Synopsis; Section 4, Objectives and Endpoints, Table 4-1	• To specify abandonment of surgery due to disease progression • • Language clarification to assess ORR	• Align the definition of an event for Event Free Survival (EFS) to be consistent with Statistical Analysis Plan (SAP) • Language updated to align with current protocol requirements
Section 9.1.1.1, Definition of Disease Recurrence; Section 9.1.1.2, Definition of Disease Progression	• Clarified definition of disease progression/recurrence	• Clarified language regarding disease progression/recurrence
Section 10.3, Statistical Analysis	• Clarified that stratum may be combined if stratum size is too small	• Clarification and alignment with statistical analysis plan
Appendix 2, Study Governance Considerations, Monitoring	• Information on remote monitoring added	• Updated to include the latest BMS standard language regarding study monitoring
Appendix 7, Response Evaluation Criteria in Solid Tumors Guidelines (Version 1.1) with BMS Modifications for Neoadjuvant Lung Study	• Clarified evaluation of Best Overall Response • • Confirmatory scan requirement for CR and PR deleted	• The assessment of Best Overall Response assessment was clarified for participants within this trial • Response evaluation criteria guidelines modified

Summary of Key Changes for Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		to align with protocol requirements

Overall Rationale for Revised Protocol 02, 11-May-2020

This revised protocol updates the stratification for PD-L1 and provides clarity to the eligibility criteria and time windows for imaging assessment. These changes apply to all patients.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Schema Section 5.1 Overall Design Section 7.2 Method of Treatment Assignment	Updated stratification categories for PD-L1 status	[redacted]
Table 2-1: Screening Procedural Outline Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments Table 2-3: Post surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments Table 2-4: Long-term Follow-up Assessments Section 9.1.2.1 Neoadjuvant and Pre-Surgical Imaging Section 9.1.2.2 Post Surgical / Preadjuvant Restaging and Adjuvant Imaging Section 9.1.2.3 Methods of Measurement	Updated language for contraindications for CT with contrast	This change provides the option to use MRI instead of CT in all body regions except chest and allows compliance with site-specific radiation protection requirements.
Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments (CA20977T) Section 9.1.2.3 Neoadjuvant and Pre-Surgical Imaging	Updated window for preoperative imaging assessment.	Window expansion provides additional guidance.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-4 Long-term Follow-up Assessments (CA2097TT)	Corrected survival status window and updated footnote	This change clarifies data collection during follow-up
Synopsis Section 5.1.2.1 Neoadjuvant / Pre-surgical Treatment Period Section 7.1.1.2Platinum-based Doublet Chemotherapy Regimens	Removed carboplatin and docetaxel regimen	
Section 5.1.2.3 Participants not receiving surgery	Updated section to clarify treatment instructions when participants do not receive surgery.	This change clarifies decision for adjuvant treatment or discontinuation based occurrence of an event/non-event.
Section 6.1 Inclusion criteria 2) Type of Participant and Target Disease Characteristics letter a)	Added requirement for multidisciplinary team evaluation and that participants with N3 nodal disease are not eligible	Provides clarity for eligibility requirements.
Exclusion Criteria 2) Prior/Concomitant Therapy letter d)	Added exclusion criteria for prior treatment with drug specifically targeting T-cell co-stimulation or checkpoint pathways	Provides clarity for eligibility requirements.
Section 7.1.1.3 Dosing Information for Platinum-based Doublet Chemotherapy	Added dosing information for Pemetrexed/Carboplatin:	Provides instructions for treatment
Table 7.4.1.2-1 Dose Modifications for Non-hematologic Toxicity	Reduced dose level if creatinine clearance < 30 mL/min	
Section 7.4.2.2 Dose Delay Criteria for Platinum-based Doublet Chemotherapy	Updated dose delay criteria for docetaxel if total bilirubin is > ULN	
Section 7.7.1 Prohibited and/or Restricted Treatments	Prohibited administration of strong CYP3A4 inhibitors with docetaxel.	

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.2 Platinum-based Doublet Chemotherapy Dose Discontinuation	• Added discontinuation for cystoid macular edema	[redacted]
9.8.1 Tumor Tissue and Blood Tissue Collection	Removed minimal residual disease, single nucleotide assessments, whole blood single nucleotide polymorphism, serum miRNA, T-cell repertoire assessments and analysis	Updated biomarker collection to align with program strategy

Overall Rationale for the Revised Protocol 01, 20-Dec-2019

The revised protocol updates the document [redacted] for modifying endpoints, adding additional chemotherapy treatment regimens, adhering to local regulations for pregnancy testing and contraceptive instructions. The revisions also updates the imaging assessments and biomarker collection. Minor edits and corrections were made in the document.

Revisions apply to all current participants and participants in the future.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page and synopsis	Added short title	Aligns with disclosure title
Synopsis Section 4 Objectives and Endpoints	• Added EFS and OS comparisons by PD-L1 status as exploratory objective • Moved safety and tolerability as secondary objective • Updated endpoint definitions • Removed exploratory endpoints from synopsis	Endpoints were modified [redacted]. Other changes were added for clarity.
Synopsis Section 5.1.2.1 Neoadjuvant / Pre-surgical Treatment Period	Added drug neoadjuvant regimens for	Chemotherapy drug regimens were updated [redacted] and

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7-1 Study Treatments for CA20977T Table 7.1-1 Selection and Timing of Dose Section 7.1.1.2 Platinum-based Doublet Chemotherapy Regimens Section 7.1.1.3 Dosing Information for Platinum-based Doublet Chemotherapy Section 7.4.1 Dose Reductions for Platinum-based Doublet Chemotherapy	• carboplatin and docetaxel regimen for squamous histology • cisplatin and docetaxel regimen for squamous histology • carboplatin and paclitaxel regimen for nonsquamous histology Updated study treatment	internal consistency in the document.
Table 2-1 Screening Procedural Outline	Added pregnancy test	Provides internal consistency in the document.
Table 2-1 Screening Procedural Outline Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments Table 2-3:Post-surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments Section 5.1.2.5 Post-surgical/Pre-adjuvant Evaluation Section 9.1.2.1 Neoadjuvant and Pre-Surgical Imaging Section 9.1.2.2 Post Surgical / Preadjuvant Restaging and Adjuvant Imaging	Updated imaging language to require PET-CT for body imaging. Updated Imaging frequency and baseline measurements Updated instructions for BICR assessments.	Imaging assessments were updated to align with study needs and to provide clarity.
Table 2-1: Screening Procedural Outline	• Updated EGFR testing • Updated staging mediastinal lymph node evaluation	EGFR testing and lymph node evaluation were updated for clarity.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: Neoadjuvant and Pre-surgery Procedures and Assessments Table 2-3:Post-surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments Section 5.1.2.5 Post-surgical/Pre-adjuvant Evaluation Section 5.1.1 Screening Section 9.8.1.1 Diagnostic/Baseline Biopsy	Updated collection of tumor tissue and surgical tumor tissue.	Instructions were expanded to collect tissue and information for central pathology review and biomarker assessments.
Table 2-4 Long-term Follow-up Assessments Section 6.1 Inclusion Criteria	Pregnancy testing and contraception use should be performed as per local regulation and approved product label.	Duration of pregnancy testing and contraception use was updated for safety.
Table 2-3:Post-surgery/Pre-adjuvant and Adjuvant Treatment Procedures and Assessments	Instruction provided for staging mediastinal lymph node.	Instructions provide clarity
Figure 5.1.2-1 Flowchart for Efficacy and Safety Data Collection Table 9.4.4-1 Clinical Laboratory Assessments Table 9.8.1-1: Biomarker Sample Schedule for All Participants	Corrected errors in data collection timing, clinical laboratory assessments, and biomarker sample.	Corrected document.
Section 5.1.2.2 Surgery	Updated instructions for preoperative mediastinal evaluation by bronchoscopy/EBUS	Change made to provide clarity.
Section 5.1.2.4 Postoperative radiotherapy as SOC	Conditions for post-operative radiation therapy were added.	Change made to provide clarity.
Section 5.1.2.5 Post surgical/Preadjuvant Evaluation	Imaging frequency and baseline measurements were updated.	Imaging modality updated for internal consistency.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.4 Disease Progression/Recurrence	Added the investigator may request PD-L1 status from screening at BICR-confirmed disease progression,	Providing the PD-L1 status will allow investigator to make treatment decisions.
Section 6.1 Inclusion Criteria	Legal authorized representatives will be allowed to sign Informed Consent where locally allowed	Language updated [redacted].
Section 6.2 Exclusion Criteria	The approved local Product Label requirements for the individual chemotherapy drugs in this trial must be followed when determining participant eligibility.	Language updated [redacted].
Section 7.3 Blinding Section 7.5 Preparation/ Handling/Storage/ Accountability Section 7.6 Treatment Compliance	Instructions for accidental blinding was updated.	Instructions for accidental blinding was updated.
Section 6.2 Exclusion Criteria Section 7.7.1 Prohibited and/or Restricted Treatments	Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment, if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.	Language updated to provide clarity.
Table 7.4.1-1 Dose Reductions for Platinum-based Doublet Chemotherapy Table 7.4.1.1-1:Dose Modifications for Hematologic Toxicity (based on Nadir Counts)	Dose modification for docetaxel was added.	Language updated [redacted].
Section 8.4.5 Preparation/Handling/Storage	Duplicate sections removed.	Duplicate sections removed.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.5.6 Treatment Compliance		
Section 9.1.1.1 Definition of Disease Recurrence Section 9.1.1.4 Definition of MPR	Definition of disease recurrence was updated for local and distant recurrence. Definition of MPR was updated. Definition of MPR was added.	Changes were made to provide clarity.
Section 9.1.2.2 Post-Surgical / Pre-adjuvant Restaging and Adjuvant Imaging	Timing of imaging assessments and baselines were updated.	Imaging modality updated to align with study needs and provide clarity.
Section 9.1.2.4 BICR Assessment of Progression	Section updated	Change made to provide clarity.
Section 9.8.1 Tumor Tissue and Blood Tissue Collection Section 9.8.1.1 Diagnostic/ Baseline Biopsy Section 9.8.2.1 Circulating tumor DNA (ctDNA)	Updated for biomarker and tissue collection	Changes made to provide internal consistency for clarity.
Appendix 2 Study Governance Considerations Appendix 6 Management Algorithms	Updated CSR and publication authoring process Added algorithm for myocarditis	Aligned with BMS standards
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized