

Official Title of Study:

Randomized, Open-Label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus
Platinum-Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage
NSCLC

(CheckMate 816: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 816)

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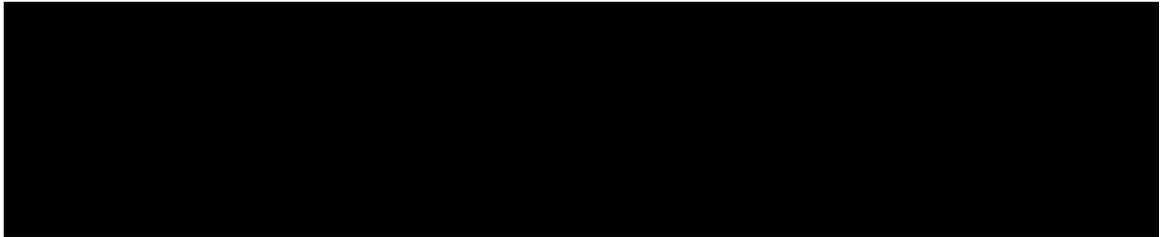
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CLINICAL PROTOCOL CA209816

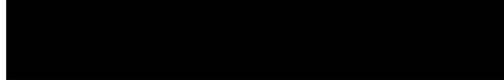
Randomized, Open-Label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus Platinum-Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage NSCLC

(CheckMate 816: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 816)

Protocol Amendment 07



24-hr Emergency Telephone Number



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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 07	18-Aug-2021	<ul style="list-style-type: none"> To account for a potential slowdown in EFS events accrual in long-term follow-up, the protocol was amended to: <ul style="list-style-type: none"> Revise EFS modeling assumptions to a piecewise exponential distribution with lower events rate in the longer term. Include one additional EFS interim analysis at 90% information fraction [REDACTED]
Revised Protocol 06	14-Jul-2020	<ul style="list-style-type: none"> Clarified EFS definition Removed the first of 2 interim analyses of EFS and updated alpha spending on the remaining interim and final analyses of EFS Clarified that the actual timing of analyses may differ from projected timing Removed text about descriptive EFS analysis
Revised Protocol 05	18-Sep-2019	<ul style="list-style-type: none"> Modified pCR analysis population and projected timelines Updated surgical approach endpoint Updated the censoring rule of TTDM No optional biopsy at disease progression collected in China. Updated Management Algorithms to include myocarditis
Revised Protocol 04	25-Jun-2019	<ul style="list-style-type: none"> Added the concomitant administration of substances that are also tubularly secreted (eg, probenecid) could potentially result in delayed clearance of pemetrexed. Added hypothesis testing for overall survival Clarified the pCR analysis population Added exploratory endpoint of Event Free Survival on next line of therapy Added instructions for BICR Updated Appendix 8 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting Adverse Events
Revised Protocol 03	21-Sep-2018	<ul style="list-style-type: none"> Enrollment in Arm A (nivolumab plus ipilimumab) was stopped Randomization of participants (1:1 ratio) into Arm C and B will continue to for a total of 350 participants Definition of event free survival is clarified. Participants with large-cell neuroendocrine carcinoma tumor histology are excluded Additional platinum doublet chemotherapy regimen (paclitaxel/carboplatin) was added

Document	Date of Issue	Summary of Changes
		<ul style="list-style-type: none"> • Dose modification for docetaxel was updated • Time to death or distant metastases (TTDM) was added to secondary endpoints. • Tumor assessments for participants who do not proceed to definitive surgery was clarified • Statistical analysis plan was updated • Rationale, background information, and trial schematic were updated • Pulmonary function parameters were clarified • Time relationship between adjuvant radiotherapy and tumor imaging assessments was clarified • Time window of Cycle 1 Day 1 end-of-infusion PK sampling for Arm A and C was clarified
Administrative Letter 03	31-Jan-2018	<ul style="list-style-type: none"> • 1. Page 19, Table 2-1 Screening Procedural Outline (CA209816), Pulmonary Function Test notes • Previously written: • Should be performed within 6 weeks prior to randomization. • Changed to: • Should be performed within 6 weeks prior to randomization. PFTs should be evaluated at screening with the following parameters: FVC, FEV1, TLC, FRC, and DLco. • • 2. Page 22, Table 2-2 Neoadjuvant Period Procedural Outline (CA209816), Pulmonary Function Test notes • Previously written: • PFTs should be re-evaluated prior to surgery only. • Changed to: • PFTs should be re-evaluated prior to surgery with the following parameters: FVC, FEV1, TLC, FRC, and DLco. • 3. Page 28, Section Table 2-4 Post-Neoadjuvant Period for Participants Receiving Adjuvant Chemotherapy (CA209816), Tumor Assessments • Previously written: • Tumor assessments using CT, with contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (\pm 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (\pm 7 days) per RECIST 1.1 for 2 years (104 weeks), then every 6 months (24 weeks \pm 7 days) for 3 years, and every year (52 weeks \pm 7 days) for 5 years or until disease recurrence or progression is confirmed by BICR. Use same imaging methods and machine of the same quality as was used at screening/baseline. • Changed to: • Tumor assessments using CT, with contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (\pm 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12

Document	Date of Issue	Summary of Changes
		<p>weeks (\pm 7 days) per RECIST 1.1 for 2 years (104 weeks), then every 6 months (24 weeks \pm 7 days) for 3 years, and every year (52 weeks \pm 7 days) for 5 years or until disease recurrence or progression is confirmed by BICR. Use same imaging methods and machine of the same quality as was used at screening/baseline.</p> <ul style="list-style-type: none"> • Adjuvant radiotherapy is allowed on study. As radiotherapy may interfere with imaging interpretation, efforts should be made to schedule radiotherapy so tumor assessments as scheduled per protocol do not cross over into the radiation period. • 4. Page 92, Table 9.5-1 Pharmacokinetic (PK) Sample Collections for Nivolumab and Ipilimumab - Arm A and Arm C Footnote d • Previously written: • No text • Added footnote: • dAs per revised protocol 02, the Cycle 1 Day 1 end-of-infusion PK sampling of nivolumab/ipilimumab in Arm A and of nivolumab in Arm C should be taken immediately, ie within 5 minutes prior to stopping the infusion of nivolumab and ipilimumab, respectively. PK sampling greater than 5 minutes before the end of infusion will be reported as a deviation.
Revised Protocol 02	06-Jul-2017	<ul style="list-style-type: none"> • Nivolumab plus platinum-doublet chemotherapy arm (Arm C) was added • The sample size was increased to 642 participants with the addition of the new treatment arm. • The primary objective was changed to multiple primary objectives of event free survival and pathological complete response; the secondary objective was changed to major pathology response. • Additional rationale and background information was provided. • Pre-screening tissue requirement was increased from minimum of 10 slides to 15 slides. • Contrast requirements for brain MRI scans were updated • Time window for pulmonary function test window was expanded from with 28 days of randomization to within 6 weeks of randomization • Synopsis was updated with exploratory objectives, endpoints, and schema. • Language in treatments administered was deleted and reference to Investigator Brochure and Pharmacy Manual was included.
Revised Protocol 01	03-Mar-2017	Incorporates Amendment 02 and Administrative Letters 01 and 02
Amendment 02	03-Mar-2017	<ul style="list-style-type: none"> • To adjust the dosing details of the chemotherapy regimens to include the dose approved by the local prescribing information and the standard of care infusion time for each country included in this study. • To expanded and to split the broad biomarker objective into 3 more detailed objectives • Clarify lymph node samples at screening and at definitive surgery

Document	Date of Issue	Summary of Changes
		<ul style="list-style-type: none"> • Clarify requirements for PET/CT scans and broadening the window of scans prior to surgery • Clarify tissue sample process for calculation of the primary endpoint • Adjust Hepatitis B Virus criteria • Added live vaccines and strong CYP3A4 inhibitors to the Prohibited Treatments • Added caution for concomitant administration of NSAIDs with pemetrexed. • Added unacceptable methods of contraception to Appendix 6
Administrative Letter 02	30-Nov-2017	<ul style="list-style-type: none"> • Clarify the correct version of the TNM Staging System. • Clarify that a minimum of 228 PD-L1+ participants will be randomized. • Clarify that physical exams, vital signs, and physical measurements should be collected prior to each dose of neoadjuvant and adjuvant therapy. • Clarify that the first post-operative tumor assessment should be performed 12 weeks (\pm 7 days) after definitive surgery. • Remove the phrase “non-protocol regimen” in regards to a non-cisplatin regimen as the protocol includes a non-cisplatin regimen option. • Clarify that weight-based dosing should be rounded up to the nearest milligram or per institutional standards. • Clarify that the EQ-5D-3L should be collected prior to Day 1 only in cycles that have multiple dosing days in each cycle.
Administrative Letter 01	31-Oct-2017	<ul style="list-style-type: none"> • To correct the IND number
Original Protocol	30-Sep-2016	Not Applicable



OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

Based on historical and emerging external data, event accrual for event-free survival (EFS) analysis is expected to slow down in long-term follow up after definitive surgery for resectable non-small-cell lung cancer (NSCLC). Recurrence dynamics after complete resection for stage I/II NSCLC show a constant recurrence rate of 6-7 events per 100 person-years of follow-up during the first 4 years, decreasing to 2 events per 100 person-year thereafter.¹ A similar slowdown was seen with stage III NSCLC. In a randomized, Phase III trial comparing neoadjuvant chemoradiation and chemotherapy both followed by surgery in stage III NSCLC, no difference was seen in progression-free survival (PFS, primary endpoint), with the PFS curves dropping sharply during the first year indicating initial high hazard rates, then flattening thereafter suggesting a markedly decreasing and stabilizing hazard rate.² Such pattern of recurrence dynamics was repeatedly seen in other neoadjuvant trials conducted in Stage I-III NSCLC.^{3,4}

Furthermore, preliminary data from recently published Phase II trials incorporating nivolumab into neoadjuvant regimens suggest potentially further decreased hazard rates for recurrence after surgery by the flattened shape of Kaplan-Meier curves of EFS/PFS. For example, in the single-arm NADIM trial of neoadjuvant nivolumab + chemotherapy followed by surgery and adjuvant nivolumab for Stage IIIA NSCLC, the 24-month PFS rate was 77.1% (95% CI 59.9-87.7), greatly exceeding historic standards.^{5,6}

To account for the aforementioned event dynamics which may preclude the necessary EFS events from accruing in a reasonable timeframe or potentially never accruing, the statistical analyses plan has been updated to model the assumptions based on a piecewise exponential distribution and incorporate a calendar-based rule in addition to the existing event-driven approach to trigger analysis timing. Moreover, one additional EFS interim analysis (IA) has been added [REDACTED] at 90% of EFS events information fraction [REDACTED]. No changes have been made to the target number of events for the existing interim and final analyses, and the overall type 1 error has been maintained. At the time of this amendment, EFS and overall survival (OS) remain blinded and have not been analyzed by the Sponsor or investigators.

SUMMARY OF KEY CHANGES OF PROTOCOL AMENDMENT 07		
Section Number and Name	Description of Change	Brief Rationale
Title Page	Updated title to “Clinical Trial Physician” and added Clinical Scientist contact information.	Updated to align with study contacts and the role name for Medical Monitor at BMS.
Section 5.3, End of Study Definition	Included additional interim analysis and calendar-based rule or the EFS final analysis.	To account for a potential slowdown in EFS event accrual in long-term follow-up in this setting.
Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Removed obsolete cross-referenced sections to the Investigator Brochure (IB).	To align with the updated IB.
Section 10.1.2, Event Free Survival (EFS)	<ul style="list-style-type: none"> Updated power calculation. Revised EFS assumptions for the control arm with piecewise exponential model. Added an additional interim analysis at 90% information fraction [REDACTED] <ul style="list-style-type: none"> Updated the timing of analyses based on a piecewise exponential model. 	To account for a potential slowdown in EFS event accrual in long-term follow-up in this setting.
[REDACTED]		
Section 10.1.4, Analyses Timing Projections	<ul style="list-style-type: none"> Revised timing projections based on updated EFS assumptions modeling and additional interim analysis included. 	To align with Sections 10.1.2 and 10.1.3 updates.
Section 10.3.3, Interim Analyses	<ul style="list-style-type: none"> Removed Table 10.1.4-1, Scheduled Analyses, Criteria, and Projected Timelines. 	
Appendix 2, Abbreviations and Trademarks	Updated the following abbreviations: <ul style="list-style-type: none"> final analysis interim analysis 	Abbreviations were updated for clarity and completeness.

References

¹ Luo F, Huang J, Sima CS et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg. 2013; 145:75-81)

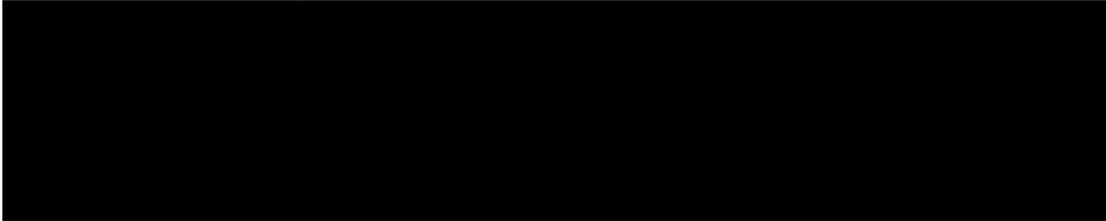
- 2 Thomas M, Rube C, Hoffknecht P et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008; 9:636-48.)
- 3 Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet* 2015; 386:1049-56.
- 4 Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *Clin Oncol* 2010 Jul 1; 28(19): 3138-45
- 5 Provencio M, Insa A, Casal-Rubio J et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020; 21:1413-22.
- 6 Cascone T, William WN, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase II randomized NEOSTAR trial. *Nat Med* 2021.27;504-14.)



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1 SYNOPSIS

Protocol Title: Randomized, Open-Label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus Platinum-Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage NSCLC

Study Phase: 3

Rationale:

Approximately 80% of lung cancer cases are non-small cell lung cancer (NSCLC), with most patients presenting with late-stage disease. At initial diagnosis, 20% of patients present with stage I or II disease, whereas 30% present with stage III disease and 50% with stage IV disease. With enhanced lung cancer screening techniques, the percentage of patients diagnosed during the early stages may increase over the duration of the trial. A standard TNM staging system is used to determine the staging for NSCLC ([Appendix 1](#)). 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 Surgical resection remains the mainstay of treatment for stage I and II patients; however, despite potentially curative surgery, approximately 50% of stage IB and 60-75% of stage 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 after adjuvant or neoadjuvant chemotherapy.

This phase 3 study, CA209816, will evaluate the clinical efficacy of nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy in operable lung cancer. Specifically, this study will compare event free survival (EFS) and compare the pathologic complete response (pCR) rate among participants with Stage IB-IIIa NSCLC treated with nivolumab plus platinum doublet chemotherapy to the EFS and pCR rates in participants treated with platinum-doublet chemotherapy.

Study Population:

1) Key Inclusion Criteria

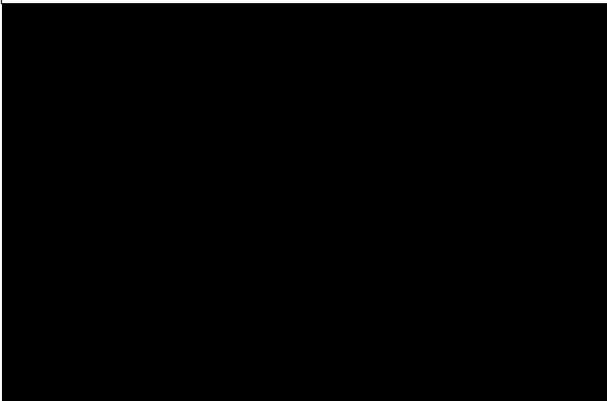
- a) Eastern Cooperative Group (ECOG) Performance Status 0-1
- b) Participants with histologically confirmed Stage IB (≥ 4 cm), II, IIIa (N2) NSCLC (per the 7th International Association for the Study of Lung Cancer) who are considered resectable
- c) Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
- d) Participants must have tumor tissue sample available for PD-L1 immunohistochemical (IHC) testing performed by a third-party analyzing lab during the screening period:
 - i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker

- evaluation prior to randomization. The tumor tissue sample may be fresh or archival if obtained within 3 months prior to enrollment.
- ii) Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies obtained by EBUS is not considered adequate for biomarker review and randomization. Core needle biopsies obtained by EBUS are acceptable for randomization.
 - e) All suspicious mediastinal lymph nodes including those that are pathologically enlarged or FDG avid on PET/CT require further sampling for pathological confirmation if accessible by EBUS, thoracoscopy, or mediastinoscopy.
- 2) Key Exclusion Criteria:
- a) Presence of locally advanced, unresectable or metastatic disease.
 - b) Participants with known EGFR mutations or ALK translocation. If testing is done, testing will be done using an FDA-approved assay and will be performed locally.

Objectives and Endpoints:

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> • To compare the event-free survival (EFS) by blinded independent central review (BICR) in participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC. 	<ul style="list-style-type: none"> • EFS defined as the length of time from randomization to any of the following events: any progression of disease precluding surgery, progression or recurrence disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Participants who don't undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 progression (based on BICR) or death.
<ul style="list-style-type: none"> • To compare the pathologic complete response (pCR) rate in participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> • pCR rate is defined as number of randomized participants with absence of residual 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.
Secondary	
<ul style="list-style-type: none"> • To assess the major pathologic response (MPR) rate by BIPR of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> • MPR rate, defined as number of randomized participants with $\leq 10\%$ residual tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group. Viable tumors in situ carcinoma should not be included in MPR calculation.

Objective	Endpoint
<ul style="list-style-type: none"> To compare the OS of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> OS is defined as the time between the date of randomization and the date of death. OS will be censored on the last date a participant was known to be alive.
<ul style="list-style-type: none"> To assess the time to death or distant metastases (TTDM) of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> 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 using BICR according to RECIST 1.1. Patients 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.
<ul style="list-style-type: none"> Exploratory 	
<ul style="list-style-type: none"> To assess clinical response rate (cRR) by BICR of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> cRR is defined as proportion of all randomized participants whose overall radiological response prior to definitive surgery is either a complete response or partial response per RECIST 1.1 criteria by BICR
<ul style="list-style-type: none"> To assess the pCR rate, MPR rate, cRR, EFS, TTDM, and OS in early-stage NSCLC participants treated with nivolumab plus platinum doublet chemotherapy compared to those treated with platinum doublet chemotherapy by PDL1 status (PD-L1 $\geq 1\%$, PD-L1 $< 1\%$/not evaluable/indeterminate) 	<ul style="list-style-type: none"> pCR rate, MPR rate, cRR, EFS, TTDM, and OS as described above
<ul style="list-style-type: none"> To assess the feasibility of surgery and rate of peri- and post-operative complications (within 90 days of surgery) in participants receiving nivolumab plus platinum doublet chemotherapy compared to participants receiving platinum doublet 	<ul style="list-style-type: none"> Proportion of delayed or canceled surgery, duration of surgery, length of hospital stay, surgical approach, including completeness of the resection, incidence of AE/SAE associated with surgery, including pneumonitis, ARDS, re-admission to the Intensive Care Unit, atrial fibrillation or other supraventricular tachycardia (SVT) to 90 days post-surgery
<ul style="list-style-type: none"> To assess the safety and tolerability of nivolumab plus platinum doublet chemotherapy compared to platinum doublet chemotherapy in early stage NSCLC 	<ul style="list-style-type: none"> Safety and tolerability will be measured by incidence of AE, SAE, immune-related AEs, deaths, and laboratory abnormalities
<ul style="list-style-type: none"> To describe the pCR rate, MPR rate, cRR, EFS, TTDM, OS, feasibility of surgery, rate of peri- and post-operative complications (within 90 days of surgery), safety and tolerability in early-stage NSCLC participants treated with nivolumab plus ipilimumab and by PDL1 status (PD-L1 $\geq 1\%$, PD-L1 $< 1\%$/not evaluable/indeterminate) 	<ul style="list-style-type: none"> pCR rate, MPR rate, cRR, EFS, OS, TTDM, feasibility of surgery, rate of peri- and post-operative complications, safety and tolerability

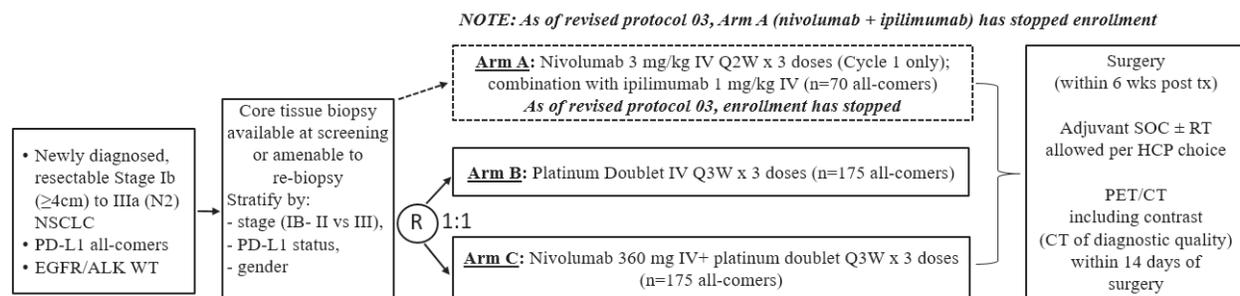
Objective	Endpoint
<ul style="list-style-type: none"> To assess pharmacokinetics of the nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy in participants with early stage NSCLC 	<ul style="list-style-type: none"> Pharmacokinetic endpoints - See Table 9.5-1
<ul style="list-style-type: none"> To assess the participant's overall health status and health utility using the 3-level version of the EQ-5D-3L visual analog scale (VAS) and utility index, respectively 	<ul style="list-style-type: none"> Change in EQ-5D-3L scores
<ul style="list-style-type: none"> To assess Event Free survival on next line of therapy (EFS2) in early-stage NSCLC participants treated with nivolumab plus platinum doublet chemotherapy compared to those treated with platinum doublet 	<ul style="list-style-type: none"> Event Free survival on next line of therapy (EFS2)
<ul style="list-style-type: none"> To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as EFS and OS) of nivolumab plus platinum doublet chemotherapy and of platinum-doublet chemotherapy, using data generated from tumor and blood (germ-line control) specimens. 	<ul style="list-style-type: none"> Biomarker endpoints - See Section 9.8.
	
<ul style="list-style-type: none"> To explore potential predictive biomarkers of nivolumab plus platinum doublet chemotherapy efficacy (such as EFS and OS) in peripheral blood and tumor specimens 	
	

Overall Design:

This is an open-label, randomized clinical trial of up to 3 cycles of neoadjuvant nivolumab (3 mg/kg every 2 weeks) and a single dose of 1 mg/kg dose of ipilimumab, up to 3 cycles of nivolumab (360 mg) plus platinum doublet chemotherapy every 3 weeks, or neoadjuvant platinum doublet chemotherapy (up to 3 cycles) in participants with early stage (Stage IB [≥ 4 cm], II, and resectable IIIA [N2]) NSCLC.

Revised protocol 03 withholds randomization into Arm A of neoadjuvant nivolumab plus ipilimumab but continues randomizing eligible participants into either neoadjuvant nivolumab plus platinum doublet chemotherapy arm or platinum doublet chemotherapy arm. Participants already randomized in the original 2-arm part (neoadjuvant nivolumab plus ipilimumab vs neoadjuvant chemotherapy) and in the arm of neoadjuvant nivolumab plus ipilimumab in 3-arm part defined by revised protocol 02 will remain in trial and continue scheduled trial procedures.

Study Schema



Endpoints

Primary: EFS and pCR rate in PD-L1 all-comers

Secondary: MPR, OS, and TTDM in PD-L1 all-comers

Exploratory: cRR in PD-L1 all-comers; pCR rate, EFS, MPR rate, OS, TTDM, and cRR by PD-L1 status. Safety, surgical feasibility, and rate of peri- and post-operative complications; PK, biomarkers, PROs

Post Surgical Assessments: CT /MRI Q12W for 2 yrs; then Q6 mos for 3 years, and every 52 weeks for 5 years thereafter until disease recurrence or PD.

Independent review for pathological and radiologic response

Eligible participants will be randomized between 2 arms in a 1:1 ratio. Participants will be stratified by:

- PD-L1 expression ($\geq 1\%$ or $<1\%$ /not evaluable/indeterminate)
- Disease stage (IB/II vs IIIA)
- Gender

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 - defined as $\geq 1\%$ tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 negative – defined as $< 1\%$ tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 not evaluable/indeterminate - defined as participants with insufficient sample quantity or quality to stain for PD-L1 status or those in whom PD-L1 status could not be determined

despite appropriate amounts of tissue sample. For the purpose of stratification, this category will be grouped with PD-L1 negative participants. No more than 10% of participants will be randomized into this category.

Tumor tissue (archival [blocks/slides \leq 3 months old] or recent tumor biopsy) must be submitted to a third-party vendor for determination of PD-L1 status testing prior to randomization.

PET/CT including contrast from the base of the skull to upper thighs will be performed at baseline (within 28 days prior to randomization) and within 14 days prior to planned definitive surgery. A separate CT, with contrast, of the chest, abdomen, and all other suspected sites of disease (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality for RECIST 1.1 measurements. Subsequent assessments (CT, including contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease.) will be performed in accordance with the Schedule of Activities. Tumor assessments must continue per protocol until disease recurrence/progression is confirmed by BICR per RECIST 1.1. Details will be outlined in the radiology manual. OS will be followed continuously every 3 months via in-person or phone contact after Post-neoadjuvant Follow-up Visit 2 or after completion of adjuvant therapy, when applicable.

Following the completion of neoadjuvant treatment, all participants who remain operative candidates will undergo definitive surgery for NSCLC. Surgery should be performed within 6 weeks after completing neoadjuvant treatment for each treatment arm.

Following definitive surgery, participants in each arm may receive adjuvant chemotherapy with or without radiation per institutional standard at the discretion of the investigator.

Number of Participants:

Approximately 350 participants will be randomized in a 1:1 ratio (175 participants in each arm) to the 2 arms (neoadjuvant nivolumab plus platinum doublet chemotherapy and platinum doublet chemotherapy) from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03.

In addition, it is expected to have around 70 participants randomized in the original 2-arm study (Arm A and Arm B) and approximately another 75 participants randomized in the arm of neoadjuvant nivolumab plus ipilimumab (Arm A) when the study had 3 arms.

Treatment Arms and Duration:

Arm A: Participants randomized into Arm A received nivolumab 3 mg/kg IV over 30 minutes every 2 weeks for up to 3 doses (ie, 6 weeks of treatment; each cycle is 14 days). In Cycle 1 Day 1 only, nivolumab will be followed by a single dose of ipilimumab 1 mg/kg IV over 30 minutes.

Arm B: Participants randomized to Arm B will receive investigator-choice of platinum doublet chemotherapy regimens in 3-week cycles up to a maximum of 3 cycles of IV chemotherapy (ie, 9 weeks of treatment; each cycle is 21 days).

- Regimen 1:
 - Vinorelbine 25 mg/m² or 30 mg/m² IV (per local prescribing information) push over 10 minutes or per institutional standard, Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard Day 1, immediately following vinorelbine
- Regimen 2:
 - Docetaxel 60 mg/m² or 75 mg/m² IV (per local prescribing information) over 60 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following docetaxel
- Regimen 3: (squamous histology):
 - Gemcitabine 1000 mg/m² or 1250 mg/m² IV (per local prescribing information) over 30 minutes or per institutional standard on Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following gemcitabine
- Regimen 4: (non-squamous histology only):
 - Pemetrexed 500 mg/m² IV over 10 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following pemetrexed
- Regimen 5:
 - Paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard on Day 1
 - Carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard on Day 1, immediately following paclitaxel

Arm C: Participants randomized into Arm C will receive nivolumab 360 mg IV + platinum doublet chemotherapy in 3-week cycles up to a maximum of 3 cycles of IV chemotherapy (ie, 9 weeks of treatment; each cycle is 21 days)

- Non-squamous NSCLC: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by pemetrexed at a dose of 500 mg/m² IV over 10 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, of a 3-week treatment cycle, for up to 3 cycles.
- Squamous NSCLC: nivolumab at a flat dose of 360 mg as 30 minute IV infusion on day 1, followed by gemcitabine at a dose of 1000 mg/m² or 1250 mg/m² (per local prescribing information) IV over 30 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, of a 3-week treatment cycle for up to 3 cycles. Gemcitabine will also be administered at a dose of 1000 mg/m² or 1250 mg/m²

as a 30 minute IV infusion or per institutional standard on day 8 of each 3-week treatment cycle.

- Any histology: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard and carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard of a 3-week treatment cycle, for up to 3 cycles

Study treatment:

Study Drug for CA209816		
Medication	Potency	IP/Non-IP
BMS-936558-01 Nivolumab	10 mg/mL	IP
Ipilimumab Solution for Injection	5 mg/mL	IP
Vinorelbine	10 mg/mL	IP
Gemcitabine	38 mg/mL	IP
Docetaxel	10 mg/mL	IP
Pemetrexed	500 mg/vial	IP
Cisplatin	1 mg/mL	IP
Carboplatin	10 mg/mL	IP
Paclitaxel	6 mg/mL	IP

Independent Data Monitoring Committee

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 CA209816. An interim DMC review will occur after 15 participants are enrolled in Arm A and after 15 participants are enrolled in Arm C and have completed surgery. 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.

Independent Radiology/Pathology Review:

Independent pathology and radiology review will be established for central review and confirmation of endpoints. Images and tumor/lymph node samples will be submitted to these third-party vendors for central review. Sites will be trained prior to enrolling the first study participant. Images and pathology samples acquisition guidelines and submission process will be outlined in the study Imaging/Laboratory Manuals to be provided by the vendors.

Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor sample in RNA later for biomarker studies (as applicable dependent on the size of the residual tumor) is mandatory on the day of surgery. RNA later sample will not be collected in China. Processing the remainder of the specimen for histopathologic analysis should be performed within 72 hours of the procedure. Sections will be used for central pathology review assessing pathologic complete response (pCR) and major pathologic response (MPR). Any tumor, tumor bed or lymph node specimens that are reviewed locally must be submitted for central pathology review. Gross examination on the entire specimen should be performed which includes all tumor, and associated lymph node tissue and uninvolved parenchyma. The specimen should be sectioned at 0.5 cm intervals, and blocks should be submitted for the full cross section for every other 0.5 cm interval. For very large tumors with no gross evidence of response, a minimum of 1 slide/cm is required for assessment of pathologic response. When estimating viable tumor, in situ carcinoma should not be included. Pathology specimen collection and processing guidelines are outlined in the CA209816 Laboratory Manual. A blinded pathology review process will be utilized to assess for confirmation of endpoints.

Radiologic tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis.

Tumor assessments will be sent to and reviewed by a Blinded Independent Central Review (BICR) from a third-party radiology vendor on an on-going basis. At the time of investigator assessed radiographic progression per RECIST 1.1, the site must request a BICR- for confirmation of progression or disease recurrence. However, BICR confirmation of progression should not be requested if investigator judges the progression will not preclude surgery. Participants should proceed to definitive surgery and tumor assessments post surgery should be continue per schedule of activities. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

Participants whose disease progression or disease recurrence is not confirmed by central review will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, even after the initiation of subsequent anti-cancer therapies. Subsequent tumor assessments must be submitted to the third party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the participant to have met RECIST 1.1 criteria for progression or disease recurrence.

Abbreviations are listed in [Appendix 2](#).

REFERENCES

- ¹ Mountain, CA. 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 (CA209816) ^a

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Informed Consent Form prior to screening for study participation. If a participant is re-enrolled, the participant must be re-consented, and eligibility should be re-confirmed. Register in Interactive Response Technology to obtain participant number.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose. Participants must also meet operative criteria (Section 9.10.1).
Medical History	X	
Tumor Tissue Samples	X	Tumor tissue submission prior to randomization is mandatory. If a recent/archived (within 3 months) biopsy sample is not available at screening, a fresh biopsy will be taken. Sufficient tumor tissue obtained prior to randomization (block or minimum of 15 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). If less than 15 slides are available, then the Medical Monitor should be contacted to advise on eligibility. For participants for whom a biopsy is not feasible, archival tumor material must be made available. Fine needle aspirate of draining lymph node is not acceptable. Core needle biopsies obtained by EBUS are acceptable. PD-L1 status must be determined prior to randomization.
Mediastinal lymph node sampling	X	All suspicious mediastinal lymph nodes including those that are pathologically enlarged or FDG avid on PET/CT require further sampling for pathological confirmation if accessible by EBUS, mediastinoscopy, or thoracoscopy.
Screening/Baseline Tumor Assessments	X	PET/CT including contrast from the base of the skull to the upper thighs, within 28 days prior to randomization. A separate CT with contrast of the chest, abdomen, and other suspected areas of disease (as well as the PET/CT) is required if the CT component of the PET/CT is not of sufficient diagnostic quality for RECIST 1.1 measurements. Participants with stage II or higher disease and those with a suspicion of brain metastasis should have a MRI or CT of the brain pre- and post-contrast within 28 days of randomization. Tumor assessments should be performed following RECIST 1.1 criteria.
Prior Medication	X	
ECOG Performance Status	X	Within 14 days prior to randomization (Appendix 3)

Table 2-1: Screening Procedural Outline (CA209816) ^a

Procedure	Screening Visit	Notes
Safety Assessments		
History and Physical Examination	X	Includes assessment of symptoms, review of system (ROS), height, weight, BSA (for platinum dosing), and full physical exam within 14 days prior to randomization.
Vital Signs and Oxygen Saturation	X	Includes body temperature, respiratory rate, and seated blood pressure, heart rate, and oxygen saturation by pulse oximetry (at rest). Obtained at the screening visit and within 72 hours prior to first dose.
Pulmonary Function Test	X	Should be performed within 6 weeks prior to randomization. Includes FVC, FEV1, TLC, FRC, and DLco.
Concomitant Medication Collection	X	Within 14 days of randomization.
Serious Adverse Events Assessment	X	Serious Adverse Events from the time of consent
Adverse Events Assessment	X	
Laboratory Tests	X	CBC w/differential, chemistry panel including: Albumin, LDH, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, phosphate, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, T4 (free), T3 (free or total) within 14 days prior to randomization. Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), reflex HBV DNA, hepatitis C antibody (HCV Ab), and reflex hepatitis C RNA (HCV RNA). Within 28 days prior to randomization.
ECG	X	ECG to be performed prior to randomization and recorded after the participant has been supine for at least 5 minutes.
Pregnancy Test	X	Urine or serum test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 14 days prior to randomization.
Study Treatment		
Randomize	X	

^a Screening assessments should occur within 28 days of randomization unless otherwise noted.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CBC complete blood count; Cl, chloride; DLco, diffusing capacity; EBUS, endobronchial ultrasound; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C antibody; ICF, informed consent form; LDH, lactate dehydrogenase, K, potassium; Mg, magnesium; NA, sodium; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; T.Bili, total bilirubin; TLC, total lung capacity; TSH, thyroid stimulating hormone.

Table 2-2: Neoadjuvant Period Procedural Outline (CA209816)

Procedure	During Treatment Visits ^{a,b}	Notes
Safety Assessments		
Physical Examination	X	Includes assessment of signs, symptoms, and ROS prior to each dose.
Vital Signs and Oxygen Saturation	X	Including BP, HR, temperature, respiratory rate, and oxygen saturation by pulse oximetry (at rest) prior to each dose.
Physical Measurements	X	Weight, Body Surface Area (for cytotoxic dosing), and ECOG status. The dosing calculations for treatment arms should be based on the body weight, except for nivolumab on Arm C, which will be administered using a flat dose of 360 mg. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the previous dose, the dose must be recalculated for the dose of the day by using the participant's weight of the day, and this updated value becomes the reference for subsequent dosing calculations. All doses should be rounded to the nearest milligram or as per institutional standard.
Serious Adverse Event Assessment	X	
Adverse Events Assessment	X	
Review of Concomitant Medications	X	
Pulmonary Function Test	See notes	PFTs should be re-evaluated prior to surgery only. Includes FVC, FEV1, TLC, FRC, and DLco.
Laboratory test	X	On-study local laboratory assessments should be done within 72 hours prior to each dose, starting with Cycle 1 Day 1 (C1D1). C1D1 labs do not need to be repeated if they were performed within 14 days of dosing. CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, albumin, and phosphate. TSH with reflexive T4 (free), T3 (free or total) for Arm A and Arm C only. Repeat every 6 weeks while receiving nivolumab.
Pregnancy Test	X	Serum or urine (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to first dose and then every 4 weeks for Arm A, every 3 weeks for Arm C, and Arm B while receiving study treatment. An extension of up to 72 hours prior to the start of study drug may be permissible in situations where results cannot be obtained within the standard 24 hours window, subject to Medical Monitor approval.

Table 2-2: Neoadjuvant Period Procedural Outline (CA209816)

Procedure	During Treatment Visits ^{a,b}	Notes
Efficacy Assessments		
Tumor Assessments	X	PET/CT including contrast of the base of the skull through the upper thighs, within 14 days prior to surgery per RECIST 1.1. A separate CT with contrast of the chest, abdomen, and all other suspected areas of disease (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality for RECIST measurements.
Pharmacokinetic Assessments		
PK samples ^c	X	Arm C only. Refer to Table 9.5-1
Biomarker Assessments		
Exploratory Biomarker	X	██████████
Patient-reported Outcomes Assessment		
EQ-5D-3L	X	For C1D1: performed after randomization PRIOR to first dose. On Day 1 of each cycle of study drug administration, the EQ-5D-3L will be administered PRIOR to treatment.
Study Treatment		
IRT Drug Vial Assignments	X	
Dispense Study treatment	X	Within 7 calendar days after randomization, the participants must receive the first dose of study medication. Participants no less than 18 days between doses for nivolumab on Arm C. If a dose is delayed for any reason, participants should be dosed no later than 7 days following a planned dose on any arm. If more than 7 days delay is needed for any reason, the intended dose should be skipped. If a participant receiving chemotherapy on a Day 1 and Day 8 schedule (ie, cisplatin/gemcitabine) is unable to receive Day 1 of chemotherapy but recovers in time to receive the Day 8 dose, the Day 8 dose of chemotherapy may be administered.
Surgery per Standard of Care	See notes	Surgery should be performed within 6 weeks after completing up to 3 cycles of neoadjuvant therapy as indicated by the institutional standard of care (SOC). Doses skipped during pre-operative treatment should not be replaced.

^a Each cycle in Arm B and Arm C is 21 days.

^b Neoadjuvant period assessments should be performed within 72 hours prior to dosing, unless otherwise noted.

^c Arm C only

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CBC complete blood count; Cl, chloride; DLco, diffusing capacity; EBUS, endobronchial ultrasound; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; HR, heart rate; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C antibody; ICF, informed consent form; IRT, interactive response technology; LDH, lactate dehydrogenase, K, potassium; Mg, magnesium; NA, sodium; PFT, pulmonary function test; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; T.Bili, total bilirubin; TLC, total lung capacity; TSH, thyroid stimulating hormone.



Table 2-3: Post-Neoadjuvant Period for Those Participants Not Receiving Adjuvant Therapy (CA209816)

Procedure	Post-Neoadjuvant Therapy Visits 1 and 2 ^a	Survival Follow-Up Visits ^{b,c}	Notes
Safety Assessments			
Physical Examination	X		Includes assessment of signs and symptoms and ROS.
Vital Signs and Oxygen Saturation	X		Include BP, HR, temperature, and oxygen saturation by pulse oximetry (at rest).
Serious Adverse Events Assessment	X		All AE/SAEs to be collected for up to 100 days after the last dose of neoadjuvant therapy or 90 days after surgery, whichever is longer.
Adverse Events Assessment	X		All AE/SAEs to be collected for up to 100 days after the last dose of neoadjuvant therapy or 90 days after surgery, whichever is longer.
Review of Concomitant Medications	X	X	Document subsequent cancer therapy
Laboratory Tests	X		CBC w/ differential, LFTs (ALTs, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, albumin, and phosphate. TSH with reflex T4 (free) and T3 (free or total) for Arm A and Arm C only. Laboratory tests should be done at Post-neoadjuvant Visit 1 and repeated at Post-neoadjuvant Visit 2 if study-related toxicity persists.
Pregnancy Test	X		Serum or urine (minimum sensitivity 25 IU/L or equivalent units of HCG)
Efficacy Assessments			
Tumor Assessments	----See Notes---		Tumor assessments with CT, including contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (± 7 days) per RECIST 1.1 for 2 years (104 weeks), then every 6 months (24 weeks ± 7 days) for 3 years, and every year (52 weeks ± 7 days) for 5 years or until disease recurrence or progression is confirmed by blinded independent central review (BICR). For participants who did not receive definitive surgery AND without tumor progression confirmed by BICR, the first tumor assessments should be done 12 weeks (± 7 days) following the tumor restaging, subsequent tumor assessments will be performed with the same frequency and methods as described for those

Table 2-3: Post-Neoadjuvant Period for Those Participants Not Receiving Adjuvant Therapy (CA209816)

Procedure	Post-Neoadjuvant Therapy Visits 1 and 2 ^a	Survival Follow-Up Visits ^{b,c}	Notes
			having received definitive surgery; in case the planned initiation of subsequent anti-cancer therapy is within 12 weeks of restaging, every effort should be made to repeat tumor assessment prior to subsequent anti-cancer therapy. Use same imaging method and a machine of the same quality as was used at screening/baseline
Pathology and Biomarker Assessments			
Tissue and biomarker assessments	--See notes--		Tissue collection from definitive surgical resection is mandatory for pathologic response assessments and highly recommended for biomarker assessments on the day of surgery. Tumor biopsy collection is optional but highly recommended from participants at disease progression. All tumor biopsy collection details will be provided in the lab manual. [REDACTED]
Patient-reported Outcomes Assessment			
EQ-5D-3L	X	X	Every 3 months after Post-neoadjuvant Visit 2 for 1 year and then once every 6 months thereafter. May be completed as a phone call if a clinic visit is not otherwise required.
Participant Survival Status			
Survival Status	X	X	Every 3 months after Post-neoadjuvant Follow-Up Visit 2. May be accomplished by visit, phone contact, or email to assess subsequent anti-cancer therapy

^a Post-neoadjuvant Visit 1 within 30 days from the last dose of neoadjuvant therapy \pm 7 days and prior to surgery (this may lead to shortened interval between last dose of neoadjuvant treatment and post-neoadjuvant visit 1). If Post-neoadjuvant Visit 1 falls within 7 days of the scheduled surgery date, then the Post-neoadjuvant Visit 1 visit may coincide with the surgery admission. All Neoadjuvant Visit 1 assessment procedures should be completed prior to surgery. Post-adjuvant Visit 2 = 70 days (\pm 7 days) from Post-neoadjuvant Visit 1. Post-neoadjuvant visits may coincide with the date of post-surgical follow-up. Timing of Post-neoadjuvant Visits 1 and 2 are based on the pre-surgical neoadjuvant treatment timelines.

^b Survival Follow-up Visits begin 3 months after Post-neoadjuvant Visit 2. Visits should occur every 3 months (\pm 7 days).

^c For those participants who have progression confirmed by BICR, participants will continue to be followed for survival status every 3 months by visit, phone contact, or email.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CBC complete blood count; Cl, chloride; DLco, diffusing capacity; EBUS, endobronchial ultrasound; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C antibody; ICF, informed consent form; LDH, lactate dehydrogenase, K, potassium; Mg, magnesium; NA, sodium; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; T.Bili, total bilirubin; TLC, total lung capacity; TSH, thyroid stimulating hormone.



Table 2-4: Post-Neoadjuvant Period for Participants Receiving Adjuvant Chemotherapy (CA209816)

Procedure	During Adjuvant Treatment Visit ^a	Post Neoadjuvant Therapy Visits 1 and 2 ^b	Survival Follow-Up Visits ^{c,d}	Notes
Safety Assessments				
Physical Measurements	X			Weight, BSA (for cytotoxic dosing), and ECOG status prior to each dose. The dosing calculations for the platinum doublet chemotherapy arm should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the previous dose, the dose must be recalculated for the dose of the day using the participant's weight of the day, and this updated value becomes the reference for subsequent dosing calculations. All doses should be rounded to the nearest milligram or per institutional standard.
Physical Examination	X	X		Includes assessment of signs, symptoms, and ROS prior to each dose.
Vital Signs and Oxygen Saturation	X	X		Include BP, HR, temperature, and oxygen saturation by pulse oximetry (at rest) prior to each dose
Serious Adverse Events Assessment	X	X		All AEs/SAEs to be collected for up to 30 days after the last dose of adjuvant therapy.
Adverse Event Assessments	X	X		All AEs/SAEs to be collected for up to 30 days after the last dose of adjuvant therapy
Review Concomitant Medication	X	X	X	Document subsequent cancer therapy.
Laboratory test	X	X		On-study local laboratory assessments should be done within 72 hours prior to each dose and at Post-neoadjuvant Visit 1. To be repeated at Post-neoadjuvant Visit 2 if study-related toxicity persists. CBC w/ differential, albumin, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, phosphate. TSH with reflex T4 (free) and T3 (free or total) for Arm A and Arm C only. To be conducted only at Post-neoadjuvant Therapy

Table 2-4: Post-Neoadjuvant Period for Participants Receiving Adjuvant Chemotherapy (CA209816)

Procedure	During Adjuvant Treatment Visit ^a	Post Neoadjuvant Therapy Visits 1 and 2 ^b	Survival Follow-Up Visits ^{c,d}	Notes
				Visit 1 and repeated at Post-Neoadjuvant Therapy Visit 2 if study-related toxicity persists.
Pregnancy test	X	X		Serum or urine (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to first dose and then every 4 weeks while receiving study treatment. An extension of up to 72 hours prior to the start of study drug may be permissible in situations where results cannot be obtained within the standard 24 hours window, subject to Medical Monitor approval.
Efficacy Assessments				
Tumor Assessments		---See Notes---		Tumor assessments using CT, with contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (\pm 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (\pm 7 days) per RECIST 1.1 for 2 years (104 weeks), then every 6 months (24 weeks \pm 7 days) for 3 years, and every year (52 weeks \pm 7 days) for 5 years or until disease recurrence or progression is confirmed by BICR. Use same imaging methods and machine of the same quality as was used at screening/baseline.
Biomarker Assessment				
Exploratory Biomarker		---See Notes---		Tumor biopsy collection is optional but highly recommended from participants at disease progression. All tumor biopsy collection details will be provided in the lab manual. 

Table 2-4: Post-Neoadjuvant Period for Participants Receiving Adjuvant Chemotherapy (CA209816)

Procedure	During Adjuvant Treatment Visit ^a	Post Neoadjuvant Therapy Visits 1 and 2 ^b	Survival Follow-Up Visits ^{c,d}	Notes
Patient-reported Outcomes Assessment				
EQ-5D-3L	X	X	X	Every 3 months after Post-neoadjuvant Visit 2 for 1 year and then once every 6 months thereafter. May be completed as a phone call if a clinical visit is not otherwise specified.
Participant Survival Status				
Survival Status	X	X	X	Every 3 months after Post-neoadjuvant Follow-Up Visit 2. May be accomplished by visit, phone contact, or email to assess subsequent anti-cancer therapy
Study Treatment				
Administer Adjuvant Chemotherapy ±PORT	X			Post-operative radiation therapy (PORT) should be administered according to standard of care.

^a Each cycle is 21 days. Assessments should be performed within 72 hours prior to dosing of adjuvant therapy.

^b Post-neoadjuvant Visit 1 within 30 days from the last dose of neoadjuvant therapy ± 7 days and prior to surgery (this may lead to shortened interval between last dose of neoadjuvant treatment and post-neoadjuvant visit 1). If Post-neoadjuvant Visit 1 falls within 7 days of the scheduled surgery date, then the Post-neoadjuvant Visit may coincide with the surgery admission. All Post-neoadjuvant Visit 1 assessment procedures should be completed prior to surgery. Post-neoadjuvant Visit 2 = 70 days (± 7 days) from Post-neoadjuvant Visit 1. Post-neoadjuvant Visit 2 may coincide with the date of post-surgical follow-up. Timing of Post-neoadjuvant Visits 1 and 2 are based on the pre-surgical neoadjuvant therapy timelines.

^c Survival Follow-up Visits begin 3 months after Post-neoadjuvant Visit 2 or after completion of adjuvant therapy, whichever occurs later. Visits should occur every 3 months (± 7 days).

^d For those participants who have progression confirmed, participants will continued to be followed for survival status every 3 months by visit, phone contact, or email.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CBC complete blood count; Cl, chloride; HR, heart rate; ECOG, Eastern Cooperative Oncology Group; DLco, diffusing capacity; EBUS, endobronchial ultrasound; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; HBcAb, Hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C antibody; ICF, informed consent form; LDH, lactate dehydrogenase, K, potassium; Mg, magnesium; NA, sodium; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; T.Bili, total bilirubin; PORT post-operative radiation therapy; TLC, total lung capacity; TSH, thyroid stimulating hormone

3 INTRODUCTION

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7 H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC).

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

Nivolumab is in clinical development for the treatment of patients with NSCLC, RCC, melanoma, squamous cell carcinoma of the head and neck (SCCHN) and other tumors (eg, glioblastoma multiforme, mesothelioma, small cell lung cancer, gastric). The combination of nivolumab and ipilimumab is in clinical development for the treatment of NSCLC, RCC, and other tumors. Opdivo® is approved in the United States (US), European Union, and other countries for the treatment of patients with unresectable or metastatic melanoma, advanced NSCLC with progression on or after platinum-based chemotherapy, advanced RCC whose disease progressed on an antiangiogenic therapy (US only), classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin treatment (US only), head and neck carcinoma (US only), and bladder cancer (US only). Opdivo is also approved in combination with Yervoy® in unresectable and metastatic melanoma.

3.1 Study Rationale

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. With enhanced lung cancer screening techniques, the percentage of those diagnosed during the early stages may increase over the duration of the trial. A standard TNM staging system is used to determine the staging for NSCLC ([Appendix 1](#)). 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 Surgical resection remains the mainstay of treatment for stage I and II patients; however, 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. Many adjuvant studies have been performed, and these trials are summarized in [Table 3.1-1](#). Although there are some conflicting results, the overall evidence from these studies suggests that adjuvant platinum doublet chemotherapy is beneficial for good Performance Status patients with stage \geq I disease. The benefit to stage IB patients is less

clear and may depend on the size of the primary tumor and other risk factors. The LACE meta-analysis of modern adjuvant and neoadjuvant trials, all of which used cisplatin-based chemotherapy, suggested a 5% absolute survival advantage at 5 years from adjuvant chemotherapy with the benefit being greatest for stage II and IIIA patients. 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.⁴

Table 3.1-1: 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%.^{2,3,5} The current available standard of care (SOC) only provides a 5% absolute improvement in 5-year overall survival (OS).^{6,7,8,9} The SOC comprises adjuvant or neoadjuvant platinum doublet chemotherapy for patients with operable stage IB-III A 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 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.^{6,7,8} Randomized trials are currently on-going to explore the potential benefit of nivolumab in the adjuvant and locally advanced unresectable NSCLC setting. In addition, the safety and efficacy profile of neoadjuvant nivolumab monotherapy or in combination (nivolumab plus ipilimumab or nivolumab plus chemotherapy) are being evaluated in ongoing trials.

The phase 3 study, CA209816, will evaluate the clinical efficacy and will establish the safety of nivolumab plus ipilimumab, especially nivolumab plus platinum doublet chemotherapy, in resectable lung cancer. Specifically, this study will compare EFS and pCR rate among participants treated with neoadjuvant nivolumab plus platinum doublet chemotherapy vs participants treated with platinum doublet chemotherapy, and will describe pCR rate and EFS for those treated with neoadjuvant nivolumab plus ipilimumab in Stage Ib-IIIa NSCLC.

3.1.1 Research Hypothesis

In participants with stage IB (≥ 4 cm), II or IIIA (N2) NSCLC considered resectable by the local multidisciplinary team, administration of neoadjuvant nivolumab plus platinum doublet chemotherapy (up to 3 cycles) has superior efficacy to neoadjuvant platinum doublet chemotherapy (up to 3 cycles).

3.2 Background

3.2.1 Indication Background

Approval of nivolumab in advanced NSCLC was based on 2 phase 3 trials (CheckMate 017 and CheckMate 057) which demonstrated survival benefit over docetaxel across histologies. The approval in squamous NSCLC was based on the results of CA209017, a randomized trial of nivolumab versus docetaxel. The median OS for patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend toward better efficacy for those with PD-L1 expressing tumors. A single-arm trial (CA209063) of 117 patients with metastatic squamous NSCLC with progression after platinum-based chemotherapy and at least 1 additional systemic regimen showed a 15% objective response rate (ORR); 59% of participants with an ORR had response durations of 6 months or longer.¹¹

The approval of nivolumab for the treatment of non-squamous NSCLC is based on a second phase 3 study, CA209057, which met its primary endpoint of superior OS of nivolumab versus docetaxel in patients with previously treated non-squamous NSCLC at a preplanned interim analysis (IA). Patients in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction P values, reported for PD-L1 expression subgroups by each of the predefined expression levels, suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36% in patients with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs docetaxel at 1%,

5% and 10% PD-L1 expression level. In contrast, no statistically significant difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor, although these patients also experienced durable responses, and the safety profile was more favorable for nivolumab vs docetaxel.¹²

Although the first-line CA209026 trial did not demonstrate that single agent nivolumab provided superior efficacy over platinum doublet chemotherapy, the efficacy of nivolumab was similar to that of chemotherapy in this first line patient population. In the ongoing study CA209012, 77 patients were treated with nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W or Q6W. Overall response rates were observed in 43% of all treated patients and in 57% and 92% of patients with $\geq 1\%$ and $\geq 50\%$ tumor PD-L1 expression, respectively. Six investigator-assessed CRs (8%) and 3 pathologic responses were observed. The median duration of response (DOR) was not reached in the overall population or subpopulations. Duration of response ranged from 1.4+ to 27.9+ months.¹³ Recent 2-year OS data in CA209012 showed survival data in all treated patients and by PD-L1 expression. All treated patients (n = 77) showed a 1 years OS of 76% and 2 year OS of 49%. When analyzed by PD-L1 expression, patients with $\geq 1\%$ PD-L1 (n = 47) had a 1 years OS of 87% and 2 year OS of 58%, which increased to 100% and 62%, respectively for $\geq 50\%$ PD-L1 patients. Nivolumab plus ipilimumab remained tolerable, as most treatment-related AEs were manageable and no new safety concerns were identified in follow-up.¹⁴

The ongoing phase 3 CheckMate 227 study enrolled patients with stage IV or recurrent NSCLC that was not previously treated. Those with a level of tumor PD-L1 expression of at least 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy; those with a tumor PD-L1 expression level of less than 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy. Tumor mutational burden was determined by the FoundationOne CDx assay. Recently, in the pre-specified analysis of patients with high tumor mutational burden at a prospective cutoff of ≥ 10 mutations/MB, progression-free survival was significantly longer in the group treated by nivolumab plus ipilimumab compared to chemotherapy, demonstrating a median PFS of 7.2 months vs 5.5 months, respectively (HR 0.58; 97.5% CI 0.41, 0.81) (Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden.¹⁵ The treatment effect was consistent in a pre-specified multi-variate analysis when adjusted for PD-L1 expression, histology, and other clinical factors. The ORR was also significantly greater for the nivolumab plus ipilimumab group (45.3% vs 26.9%; treatment difference 18.4%; 95% CI (7.6, 28.8), and the responses appeared durable with 68% of responses ongoing after 1 year and the DOR not reached (95% CI 12.2, NR) compared to 5.4 months (95% CI 4.2, 6.9) for chemotherapy. In patients with TMB <10 mut/Mb, ORR was 24.6% in nivolumab plus ipilimumab arm and 25.9% in chemotherapy arm, HR for PFS being 1.07 (95% CI: 0.84, 1.35). In all randomized patients (irrespective of TMB or PD-L1 status), 1-year PFS was also higher with nivolumab plus ipilimumab than with chemotherapy [30.9% vs 17%; HR 0.83 (95% CI, 0.72 to 0.96)]. The rate of grade 3 or 4 treatment-related adverse events in all treated population (regardless of TMB or PD-L1 status) was 31.2% with nivolumab plus ipilimumab and 36.1% with chemotherapy, it was

slightly higher with nivolumab plus ipilimumab in patients with high TMB tumor (37%), but the safety profile was overall consistent with previously reported data with no new safety signals.

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naïve subjects with advanced NSCLC in CA209012.¹⁶ Nivolumab 10 mg/kg was combined with gemcitabine and cisplatin or pemetrexed and cisplatin. Nivolumab 10 mg/kg and 5 mg/kg was combined with paclitaxel and carboplatin. The safety profile of nivolumab plus platinum-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 overall response rate across all the nivolumab and chemotherapy cohorts range from 33-47% and median duration of response was 27.3 weeks. The 1-year survival rate for all cohorts combined is 71%.

In the ongoing CheckMate 227 trial, data in patients with tumor of <1% PD-L1 expression became also available recently.¹⁷ 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]), mPFS of nivolumab plus ipilimumab was 4.4 months (95%CI: 3.1 to 6.0). ORR was 36.7% in nivolumab plus chemotherapy arm, 23.1% in chemotherapy arm, and 25.1% in nivolumab plus ipilimumab arm. mDOR was 7.2 months in nivolumab plus chemotherapy arm, 4.7 months in chemotherapy arm, and 18.0 months in nivolumab plus ipilimumab arm. The rate of grade 3 or 4 treatment-related adverse events was 52% with nivolumab plus chemotherapy, 35% with chemotherapy, and 25% with nivolumab plus ipilimumab, overall, for nivolumab plus chemotherapy, the safety profile and efficacy are consistent with previously reported data as well as data from other PD-(L)1 blockades in combination with chemotherapy.

Both nivolumab plus ipilimumab and nivolumab plus chemotherapy compare favorably in terms of the expected clinical benefit including response rate and overall survival observed with platinum doublet chemotherapy in first line NSCLC. These data suggest that nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy have the potential to provide superior pathologic response and event-free survival compared to platinum doublet chemotherapy as neoadjuvant therapy in early-stage NSCLC.¹⁸

In general, nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy is well tolerated, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action. Nivolumab plus ipilimumab and nivolumab plus platinum doublet chemotherapy are currently in phase 3 development in the first-line metastatic and as monotherapy in the early stage NSCLC settings.

As neoadjuvant therapy, in Stage I-III NSCLC, in ongoing phase 2 trial (Section 5.4.3) nivolumab as monotherapy showed promising anti-tumor activity in terms of depth of pathological response while the potential benefit of neoadjuvant nivolumab plus ipilimumab are still under study. On the other hand, preliminary data from ongoing phase 2 trial (NADIM, Section 5.4.3) of neoadjuvant nivolumab plus platinum 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 with little adverse impact to the feasibility of surgery. The platinum 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.

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

3.2.2 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.^{19,20,21} 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.²² 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.²³ 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 has 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.²⁴ 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 \pm 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 CMV restimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN- γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).²⁵

3.2.3 *Ipilimumab Mechanism of Action*

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.²⁶ Ipilimumab is a fully human monoclonal IgG1 κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.4 *Nivolumab Combined with Ipilimumab Clinical Activity*

CA209012 (Checkmate 012) is a multi-arm phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced NSCLC, as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of objective response rates (ORR) and 24-week PFS. Exploratory endpoints included OS and efficacy by PD-L1 expression. In the study, patients were tested for PD-L1 and 69% had evaluable PD-L1 expression. Participants were enrolled to receive nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W or Q6W (n = 77), and nivolumab 3 mg/kg Q2W (n = 52). ORR was 43% in all treated patients and 57% and 92% in patients with $\geq 1\%$ and $\geq 50\%$ tumor PD-L1 expression, respectively, 6 investigator-assessed CRs (8%); including 3 pathologic responses were achieved in the nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W/Q6W cohorts. The median duration of response (DOR) was not reached in the overall population or subpopulations. Duration of response ranged from 1.4+ to 27.9+ months.

The rate of treatment-related adverse events in the Q12W/Q6W (79%) arms were comparable to monotherapy (73%). In the study, Grades 3 to 4 AEs were 36% and 19% for the Q12W/Q6W and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs led to discontinuation in 8% and 12% of patients in the Q12W/Q6W cohorts and nivolumab monotherapy arms, respectively. There were no treatment-related deaths. The treatment-related select AEs in patients across all treatment arms were skin-related (31%), gastrointestinal (19%), endocrine (18%), and pulmonary (6%).

As described in [Section 3.2.1](#), ongoing phase 3 CheckMate 227 study randomized patients with stage IV or recurrent NSCLC that was not previously treated in various study treatment arms by tumor PD-L1 status. Recently, in the pre-specified analysis of patients with high tumor mutational burden at a prospective cutoff of ≥ 10 mutations/MB, progression-free survival was significantly longer in the group treated by nivolumab plus ipilimumab compared to chemotherapy, HR of PFS being 0.58 (97.5% CI 0.41, 0.81). The treatment effect was consistent and independent of PD-L1 expression, or histology. The ORR was also significantly greater for the nivolumab plus ipilimumab group (45.3% vs 26.9%) and the responses appeared more durable with median DoR not reached (95% CI 12.2, NR) compared to 5.4 months (95% CI 4.2, 6.9) for chemotherapy. In patients with TMB <10 mut/Mb, similar efficacy was seen in terms of PFS and ORR between nivolumab plus ipilimumab and chemotherapy. The safety profile was overall consistent with

previously reported data with no new safety signals. In another readout focusing on patients with tumor of <1% PD-L1 expression, nivolumab plus ipilimumab showed similar efficacy to chemotherapy in terms of PFS and ORR but with much longer DoR, with a consistent safety profile of previously reported data.

As of revised protocol 03, the nivolumab plus ipilimumab has stopped enrollment.

3.2.5 **Immuno-oncology Treatment Combined with Chemotherapy Clinical Activity**

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.¹³ 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 have also been shown to reduce MDSCs and hence interferon-gamma, which have inhibitory roles in the immune response.^{27,28} The dual role of cytotoxicity and immune activation from chemotherapy has provided the biological rationale for the development of combinations with immunotherapy.²⁹

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naïve 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 was combined with paclitaxel and carboplatin.

The safety profile of nivolumab plus platinum-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 subjects (13%): Grade 3-4 in 4 subjects (7%). Twelve (21%) subjects discontinued due to treatment-related AEs (Table 3.2.5-1).

Table 3.2.5-1: Safety in CA209012

	All Grades	Total (N=56)	
		Grade 3	Grade 4
Subjects 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

Table 3.2.5-1: Safety in CA209012

	Total (N=56)		
	All Grades	Grade 3	Grade 4
Nausea	46 (26)	2 (1)	0
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 3.2.5-2). Activity was evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors. Overall, 79% (44/56) of subjects had evaluable tumor samples. At the $\geq 1\%$ 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 3.2.5-2: Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012

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	27.3	27.3
12-mo OS rate, %	50	87	72	86
18-mo OS Rate, %	33	60	40	62
Median OS, Weeks	51	83	65	Not Reached

As described in [Section 3.2.1](#) 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]), mPFS of nivolumab plus ipilimumab was 4.4 months (95%CI: 3.1 to 6.0). ORR was 36.7% in nivolumab plus chemotherapy arm, 23.1% in chemotherapy arm, and 25.1% in nivolumab plus ipilimumab arm. mDOR was 7.2 months in nivolumab plus chemotherapy arm, 4.7 months in chemotherapy arm, and 18.0 months in nivolumab plus ipilimumab arm. The rate of grade 3 or 4 treatment-related adverse events was 52% with nivolumab plus chemotherapy, 35% with chemotherapy, and 25% with nivolumab plus ipilimumab. 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.

3.3 Benefit/Risk Assessment

The early-stage (IB-III) 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 doublet chemotherapy, only provides a 5% absolute improvement in 5-year OS.

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 participants with operable NSCLC. A meta-analysis based on 7 trials involving 988 participants suggested that neoadjuvant chemotherapy improved OS when given preoperatively in a similar magnitude to those observed with adjuvant chemotherapy. Several studies have also shown preoperative cytotoxic chemotherapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality.

The clinical activity of nivolumab observed to date in NSCLC, including 2 positive phase 3 studies demonstrating prolonged survival with nivolumab monotherapy compared to docetaxel in squamous and non-squamous NSCLC after platinum failure, suggests the potential for improved clinical outcomes. CA209057 (non-squamous NSCLC) study demonstrated OS was superior for participants receiving nivolumab compared to those receiving docetaxel. In this study, interaction P values reported for PD-L1 expression subgroups by each of the pre-defined expression levels suggested a clinically important signal of a predictive association. Higher confirmed ORRs in PD-L1 expressors were seen in the combination arm compare to the nivolumab monotherapy arm in CA209012. Based on these data, CA209816 will stratify participants based on PD-L1 status, disease stage at randomization, and gender.

In CA209012, nivolumab plus ipilimumab provides a higher ORR (43%) than nivolumab alone.^{27,30} In first-line metastatic NSCLC, this regimen also provided encouraging overall survival, with an acceptable safety profile. Combination of anti-PD1 plus chemotherapy has also shown encouraging ORR and PFS with an acceptable safety profile compared to platinum doublet chemotherapy in first-line metastatic NSCLC. These data support our belief that combination of nivolumab with ipilimumab or platinum doublet chemotherapy will demonstrate superior benefit over platinum chemotherapy doublets in the neoadjuvant setting with an acceptable safety profile.

In general, nivolumab is well tolerated, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action. Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (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.

The ongoing phase 3 CheckMate 227 study randomized patients with stage IV or recurrent NSCLC not previously treated in various study treatment arms by tumor PD-L1 status. Recently, in the pre-specified analysis of patients with high tumor mutational burden at a prospective cutoff of ≥ 10 mutations/MB, PFS was significantly longer in the group treated by nivolumab plus ipilimumab compared to chemotherapy, HR of PFS being 0.58 (97.5% CI 0.41, 0.81). The treatment effect was consistent and independent of PD-L1 expression, or histology. The ORR was also significantly greater for the nivolumab plus ipilimumab group (45.3% vs 26.9%) and the responses appeared more durable with median DoR not reached (95% CI 12.2, NR) compared to 5.4 months (95% CI 4.2, 6.9) for chemotherapy. In patients with TMB <10 mut/Mb, similar efficacy was seen in terms of PFS and ORR between nivolumab plus ipilimumab and chemotherapy. The safety profile was overall consistent with previously reported data with no new safety signals. In another readout focusing on patients with tumor of $<1\%$ PD-L1 expression, nivolumab plus ipilimumab showed similar efficacy to chemotherapy in terms of PFS and ORR but with much longer DoR, the safety profile was consistent with previously reported data.

In the setting of first line NSCLC with $<1\%$ tumor PD-L1 expression in the ongoing CheckMate 227 trial, 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]), mPFS of nivolumab plus ipilimumab was 4.4 months (95%CI: 3.1 to 6.0). ORR was 36.7% in nivolumab plus chemotherapy arm, 23.1% in chemotherapy arm, and 25.1% in nivolumab plus ipilimumab arm. mDOR was 7.2 months in nivolumab plus chemotherapy arm, 4.7 months in chemotherapy arm, and 18.0 months in nivolumab plus ipilimumab arm. The rate of grade 3 or 4 treatment-related adverse events was 52% with nivolumab plus chemotherapy, 35% with chemotherapy, and 25% with nivolumab plus ipilimumab, overall, for nivolumab plus chemotherapy, the safety profile and efficacy are consistent with previously reported data as well as data from other PD-(L)1 blockades in combination with chemotherapy.

As described in [Section 3.2.1](#), two ongoing phase 2 trials with nivolumab as monotherapy and nivolumab in combination with chemotherapy showed promising anti-tumor activity in terms of depth of pathological response without adverse impact on surgical results. Nivolumab and ipilimumab as neoadjuvant therapy remain under study, with data pending.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in [Appendix 4](#). Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. Extensive details on the safety profile of nivolumab and ipilimumab are available in the respective Investigator Brochures and will not be repeated herein.

The potential benefit of nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy as neoadjuvant therapy in Stage I-III NSCLC are not yet known. The platinum 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.

In order to assess the potential benefit of nivolumab plus platinum doublet chemotherapy over platinum doublet chemotherapy as neoadjuvant therapy in Stage I-III resectable NSCLC, this trial will randomize participants to 2 arms: nivolumab plus platinum doublet chemotherapy, or platinum doublet chemotherapy alone. Under revised protocol 02, participants already enrolled in the original 2-arm part and in the arm of nivolumab plus ipilimumab in the 3-arm part per revised protocol 02 will continue scheduled trial procedures. To assure an ongoing favorable risk/benefit assessment for participants enrolled onto CA209816, an independent Data Monitoring Committee (DMC) will be utilized to monitor the safety and activity of the treatments throughout the conduct of the trial.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the event-free survival (EFS) by blinded independent central review (BICR) in participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> EFS defined as the length of time from randomization to any of the following events: any progression of disease precluding surgery, progression or recurrence disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Participants who don't undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 (based on BICR) progression or death.
<ul style="list-style-type: none"> To compare the pathologic complete response (pCR) rate in participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> pCR rate is defined as number of randomized participants with absence of residual tumor in lung and lymph nodes as evaluated by blinded independent pathological review (BIPR), divided by the number of randomized participants for each treatment group.
Secondary	
<ul style="list-style-type: none"> To assess the major pathologic response (MPR) rate by BIPR of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> MPR rate, defined as number of randomized participants with $\leq 10\%$ residual tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group. Viable tumors in situ carcinoma should not be included in MPR calculation.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
<ul style="list-style-type: none"> To compare the OS of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> OS is defined as the time between the date of randomization and the date of death. OS will be censored on the last date a participant was known to be alive.
<ul style="list-style-type: none"> To assess the time to death or distant metastases (TTDM) of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> 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 using BICR according to RECIST 1.1. Patients 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.
Exploratory	
<ul style="list-style-type: none"> To assess clinical response rate (cRR) by BICR of participants receiving nivolumab plus platinum doublet chemotherapy vs participants receiving platinum doublet chemotherapy in operable stage IB (≥ 4 cm), II, or resectable IIIA (N2) NSCLC 	<ul style="list-style-type: none"> cRR is defined as proportion of all randomized participants whose overall radiological response prior to definitive surgery is either a complete response or partial response per RECIST 1.1 criteria by BICR
<ul style="list-style-type: none"> To assess the pCR rate, MPR rate, cRR, EFS, TTDM and OS in early-stage NSCLC participants treated with nivolumab plus platinum doublet chemotherapy compared to those treated with platinum doublet chemotherapy by PDL1 status (PD-L1 $\geq 1\%$, PD-L1 $< 1\%$ /not evaluable/ indeterminate) 	<ul style="list-style-type: none"> pCR rate, MPR rate, cRR, EFS, TTDM, and OS as described above
<ul style="list-style-type: none"> To assess the feasibility of surgery and rate of peri- and post-operative complications (within 90 days of surgery) in participants receiving nivolumab plus platinum doublet chemotherapy compared to participants receiving platinum doublet 	<ul style="list-style-type: none"> Proportion of delayed or canceled surgery, duration of surgery, length of hospital stay, surgical approach including completeness of surgery, incidence of AE/SAE associated with surgery, including pneumonitis, ARDS, re-admission to the Intensive Care Unit, atrial fibrillation or other supraventricular tachycardia (SVT) to 90 days post-surgery
<ul style="list-style-type: none"> To assess the safety and tolerability of nivolumab plus platinum doublet chemotherapy compared to platinum doublet chemotherapy in early stage NSCLC 	<ul style="list-style-type: none"> Safety and tolerability will be measured by incidence of AE, SAE, immune-related AEs, deaths, and laboratory abnormalities
<ul style="list-style-type: none"> To describe the pCR rate, MPR rate, cRR, EFS, OS, TTDM, feasibility of surgery, rate of peri- and post-operative complications (within 90 days of surgery), safety and tolerability in early-stage NSCLC participants treated with nivolumab plus ipilimumab and by PDL1 status (PD-L1 $\geq 1\%$, PD-L1 $< 1\%$ /not evaluable/indeterminate) 	<ul style="list-style-type: none"> pCR rate, MPR rate, cRR, EFS, OS, TTDM, feasibility of surgery, rate of peri- and post-operative complications, safety and tolerability as described above

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
<ul style="list-style-type: none"> To assess pharmacokinetics of the nivolumab plus ipilimumab or nivolumab plus platinum doublet chemotherapy in participants with early stage NSCLC 	<ul style="list-style-type: none"> Pharmacokinetic endpoints (See Section 9.5)
<ul style="list-style-type: none"> To assess the participant’s overall health status and health utility using the 3-level version of the EQ-5D-3L visual analog scale (VAS) and utility index, respectively 	<ul style="list-style-type: none"> Change in EQ-5D-3L scores
<ul style="list-style-type: none"> To assess Event Free survival on next line of therapy (EFS2) in early-stage NSCLC participants treated with nivolumab plus platinum doublet chemotherapy compared to those treated with platinum doublet 	<ul style="list-style-type: none"> Event Free survival on next line of therapy (EFS2)
<ul style="list-style-type: none"> To evaluate tumor mutation burden as a potential predictive biomarker of efficacy (such as EFS and OS) of nivolumab plus platinum doublet chemotherapy and of platinum-doublet chemotherapy, using data generated from tumor and blood (germ-line control) specimens. 	<ul style="list-style-type: none"> Biomarker endpoints (See Section 9.8)
<div style="background-color: black; height: 93px; width: 100%;"></div>	
<ul style="list-style-type: none"> To explore potential predictive biomarkers of nivolumab plus platinum doublet chemotherapy efficacy (such as EFS and OS) in peripheral blood and tumor specimens <div style="background-color: black; height: 63px; width: 100%;"></div>	
<div style="background-color: black; height: 163px; width: 100%;"></div>	

5 STUDY DESIGN

5.1 Overall Design

This is an open-label, randomized clinical trial of up to 3 cycles of neoadjuvant nivolumab (3 mg/kg every 2 weeks) and a single dose of 1 mg/kg dose of ipilimumab, nivolumab 360mg flat dose plus platinum doublet chemotherapy (up to 3 cycles), or platinum doublet chemotherapy (up

to 3 cycles) as neoadjuvant treatment in participants with early stage (Stage IB [≥ 4 cm], II, and resectable IIIA [N2]) NSCLC.

The original study design (before revised protocol 02) had two arms. After signing the informed consent form and upon confirmation of the participant's eligibility, participants were randomized in an open-label fashion (1:1 ratio) to either neoadjuvant nivolumab plus ipilimumab or platinum doublet chemotherapy.

Revised protocol 02 added a new, neoadjuvant nivolumab plus platinum doublet chemotherapy arm. When the third arm had opened and as each site had received IRB/EC approval of revised protocol 02, the IRT switched to a 1:1:1 randomization at the respective site. Starting from that point on, the sites were only enrolling under revised protocol 02.

Revised protocol 03 withholds randomization into the arm of neoadjuvant nivolumab plus ipilimumab but continues randomizing eligible participants into either neoadjuvant nivolumab plus platinum doublet chemotherapy arm or platinum doublet chemotherapy arm. Participants already randomized in the original 2-arm part (neoadjuvant nivolumab plus ipilimumab vs neoadjuvant chemotherapy) and in the arm of neoadjuvant nivolumab plus ipilimumab in 3-arm part defined by revised protocol 02 will remain in trial and continue scheduled trial procedures.

Participants will be randomized between 2 arms in a 1:1 ratio to neoadjuvant nivolumab plus platinum doublet chemotherapy or platinum doublet chemotherapy. Eligible participants will be stratified by:

- PD-L1 expression ($\geq 1\%$ or $< 1\%$ /not evaluable/indeterminate)
- Disease stage (IB/II vs IIIA)
- Gender

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 - defined as $\geq 1\%$ tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 negative – defined as $< 1\%$ tumor cell membrane staining positive in a minimum of 100 evaluable tumor cells
- PD-L1 not evaluable/indeterminate - defined as participants with 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. For the purpose of stratification, this category will be grouped with PD-L1 negative participants. No more than 10% of participants enrolled in this trial will be PD-L1 not evaluable/indeterminate category.

Screening begins by establishing the participant's initial eligibility and signing of the informed consent (ICF). Tumor tissue (archival [slides/block ≤ 3 month] or recent tumor biopsy) must be submitted to a third-party vendor for determination of PD-L1 status prior to randomization.

All screening assessments and procedures must be performed in accordance with [Table 2-1](#).

The Treatment Phase begins when the randomization call is made into the Interactive Response Technology (IRT). The participant will be randomly assigned to 1 of the 2 treatment arms: Arm B or Arm C. The first dose of study treatment must begin within 7 days of randomization.

- **Arm A treatment:** Participants randomized into Arm A received nivolumab 3 mg/kg IV over 30 minutes every 2 weeks for up to 3 doses (ie, 6 weeks of treatment; each cycle is 14 days). With Cycle 1 only, nivolumab was followed by a single dose ipilimumab 1 mg/kg IV over 30 minutes.
- **Arm B treatment:** Participants randomized into Arm B will receive investigator-choice platinum doublet chemotherapy in 3-week cycles up to a maximum of 3 cycles (ie, 9 weeks of treatment; each cycle is 21 days):
 - Regimen 1:
 - Vinorelbine 25 mg/m² or 30 mg/m² IV (per local prescribing information) push over 10 minutes or per institutional standard on Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following vinorelbine
 - Regimen 2:
 - Docetaxel 60 mg/m² or 75 mg/m² IV (per local prescribing information) over 60 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following docetaxel
 - Regimen 3 (squamous histology):
 - Gemcitabine 1000 mg/m² or 1250 mg/m² (per local prescribing information) IV over 30 minutes or per institutional standard on Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following gemcitabine
 - Regimen 4 (non-squamous histology only):
 - Pemetrexed 500 mg/m² IV over 10 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following pemetrexed
 - Regimen 5:
 - Paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard on Day 1
 - Carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard on Day 1, immediately following paclitaxel

Arm C treatment: Participants randomized into Arm C will receive nivolumab 360 mg IV plus platinum doublet chemotherapy in 3-week cycles up to a maximum of 3 cycles of chemotherapy (ie, 9 weeks of treatment; each cycle is 21 days)

- Non-squamous NSCLC: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by pemetrexed at a dose of 500 mg/m² IV over 10 minutes or per institutional standard and cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard of a 3-week treatment cycle, for up to 3 cycles.
- Squamous NSCLC: nivolumab at a flat dose of 360 mg as 30 minute IV infusion on Day 1, followed by gemcitabine at a dose of 1000 mg/m² or 1250 mg/m² (per local prescribing information) for a 30 minute IV infusion or per institutional standard and cisplatin at a dose of 75 mg/m² as a 120-minute IV infusion or per institutional standard, of a 3-week treatment cycle for up to 3 cycles. Gemcitabine will also be administered at a dose of 1000 mg/m² or 1250 mg/m² as a 30 minute IV infusion or per institutional standard on day 8 of each 3-week treatment cycle.
- Any histology: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard and carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard of a 3-week treatment cycle, for up to 3 cycles.

Within 7 days of randomization, the participants must receive the first dose of study medication. Participants may be dosed no less than 12 days between nivolumab doses in Arm A and no less than 18 days between nivolumab doses in Arm C. If a dose is delayed for any reason, participants should be dosed no later than 7 days following a planned dose on any arm. If more than 7 days delay is needed for any reason, the intended dose should be skipped. If a participant receiving chemotherapy on a Day 1 and Day 8 schedule (ie, cisplatin/gemcitabine) is unable to receive Day 1 of chemotherapy but recovers in time to receive the Day 8 dose, the Day 8 dose of chemotherapy may be administered. Doses that are skipped or missed will not be replaced. Surgery should be performed within 6 weeks after completing up to 3 cycles (last dose) of neoadjuvant treatment as indicated by the institutional SOC.

- For participants who are unable to tolerate cisplatin, the reasons for intolerability should be documented. If the investigator would like to use a carboplatin-containing regimen, the investigator should discuss this with and obtain approval from the Medical Monitor prior to utilization, except for opting for carboplatin plus paclitaxel.
- Carboplatin will be administered at a dose of AUC 5 or 6 as a 30-minute IV infusion or per institutional standard, on Day 1 of each 3-week cycle.
- Carboplatin should be given following gemcitabine, docetaxel, vinorelbine, pemetrexed, or 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.

All Arms

PET/CT including contrast from the base of the skull to upper thighs will be performed at baseline (within 28 days prior to randomization) and within 14 days prior to planned definitive surgery. A separate CT, with contrast, of the chest, abdomen, and all other suspected sites of disease (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality for RECIST 1.1 measurements. Subsequent radiologic assessments CT, with contrast, of the chest including adrenal glands and CT or MRI of other additional suspected/known sites of disease will be performed in accordance with [Table 2-3](#) and [Table 2-4](#). Tumor assessments must continue per protocol until disease recurrence/progression is confirmed by BICR per RECIST 1.1 ([Appendix 5](#)), even after the initiation of subsequent anti-cancer therapies. Exceptions are cases where disease progression does not preclude surgery, regardless of whether it has been confirmed by BICR, participants should proceed to definitive surgery and continue to get tumor assessments per [Table 2-3](#) and [Table 2-4](#). Tumor assessments should be done as per [Table 2-3](#) for those who did not get definitive surgery. Pharmacokinetics assessments are described in [Section 9.5](#), and biomarker assessments are described in [Section 9.8](#). OS will be followed continuously every 3 months via in-person or phone contact after Post-neoadjuvant Follow-up Visit 2 or after completion of adjuvant therapy, when applicable.

Following the completion of neoadjuvant treatment, all participants who remain operative candidates will undergo definitive surgery for their NSCLC within 6 weeks after completing neoadjuvant treatment.

Prior to surgery, any treatment-related toxicity should have resolved to \leq Grade 1 or returned to baseline (except for alopecia, fatigue, and neuropathy). Investigators should discuss residual endocrine toxicities or mild renal impairment with the Medical Monitor.

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. Study drug dose omission or delays due to AEs will not be replaced for either arm, and participants should proceed to surgery within the predefined timeframe after standard preoperative evaluation. Surgical complications occurring within 90 days of surgery will be documented and followed until resolution.

All AEs and SAEs will be documented for a minimum of 100 days after the last dose of neoadjuvant therapy or 90 days post-surgery, whichever is longer, and for 30 days after the last dose of adjuvant therapy in participants who receive adjuvant therapy.

Following definitive surgery, participants in each arm may receive up to 4 cycles of adjuvant chemotherapy with or without radiation per institutional standard at the discretion of the investigator. Investigators may choose from the following post-operative regimens:

- Regimen 1:
 - Vinorelbine 25 mg/m² or 30 mg/m² IV (per local prescribing information) push over 10 minutes or per institutional standard on Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following vinorelbine
- Regimen 2:
 - Docetaxel 60 mg/m² or 75 mg/m² IV (per local prescribing information) over 60 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following docetaxel
- Regimen 3 (squamous histology):
 - Gemcitabine 1000 mg/m² or 1250 mg/m² IV (per local prescribing information) over 30 minutes or per institutional standard on Days 1 and 8
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following gemcitabine
- Regimen 4 (non-squamous histology only):
 - Pemetrexed 500 mg/m² IV over 10 minutes or per institutional standard on Day 1
 - Cisplatin 75 mg/m² IV over 120 minutes or per institutional standard on Day 1, immediately following pemetrexed
- Regimen 5:
 - Paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard on Day 1
 - Carboplatin AUC5 or 6 IV over 30 minutes or per institutional standard on Day 1, immediately following paclitaxel

For participants who are unable to tolerate cisplatin, the reasons for intolerability should be documented. If the investigator would like to use a carboplatin regimen, the investigator should discuss this with and obtain approval from the Medical Monitor prior to utilization, except for opting for carboplatin plus paclitaxel.

Postoperative chemotherapy should not commence until pre-operative, treatment-related toxicity has returned to baseline or resolved to ≤ Grade 1 (exceptions for fatigue, alopecia, and neuropathy). Investigators should discuss residual endocrine toxicities or mild renal impairment with the Medical Monitor.

Assessments during adjuvant therapy are outlined in [Table 2-4](#).

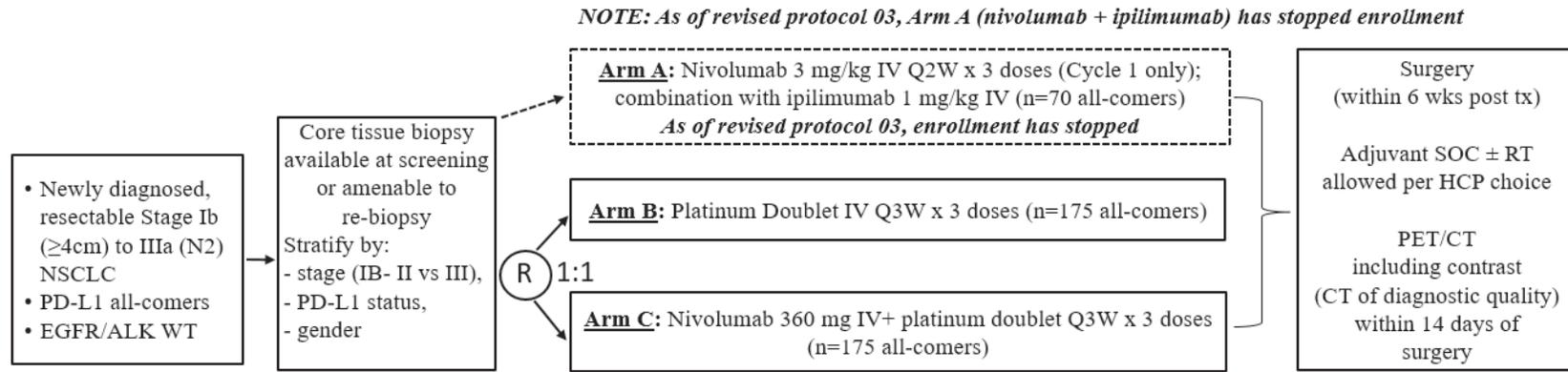
Post-operative radiation should be administered per institutional standard of care. As radiation may interfere with imaging interpretation, efforts should be made to schedule radiotherapy so that scheduled tumor assessments do not cross over into the radiation period.

The Survival Follow-Up Phase begins 3 months after post-neoadjuvant Follow-up Visit 2 or after completion of adjuvant therapy, when applicable. Participants will be followed every 3 months for survival. Survival follow-up visits may be performed by phone contact or office visit.

The study design schematic is presented in [Figure 5.1-1](#).



Figure 5.1-1: Study Design Schematic



Endpoints

Primary: EFS and pCR rate in PD-L1 all-comers

Secondary: MPR, OS, and TTDM in PD-L1 all-comers

Exploratory: cRR in PD-L1 all-comers; pCR rate, EFS, MPR rate, OS, TTDM, and cRR by PD-L1 status. Safety, surgical feasibility, and rate of peri- and post-operative complications; PK, biomarkers, PROs

Post Surgical Assessments: CT /MRI Q12W for 2 yrs; then Q6 mos for 3 years, and every 52 weeks for 5 years thereafter until disease recurrence or PD.

Independent review for pathological and radiologic response

5.1.1 Data Monitoring Committee and Other External Committees

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

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 CA209816. An interim DMC review will occur after 15 participants have enrolled into Arm A and after 15 participants have enrolled into Arm C and have completed surgery. 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.

Independent Radiology/Pathology Review

Independent pathology and radiology review will be established for central review and confirmation of endpoints. Images and tumor/lymph node samples will be submitted to these third-party vendors for central review. Sites will be trained prior to enrolling the first study participant. Images and pathology samples acquisition guidelines and submission process will be outlined in the study Imaging/Laboratory Manuals to be provided by the vendors.

Independent Pathology Review: Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor sample in RNAlater for biomarker studies (as applicable dependent on size of residual tumor) is mandatory on the day of surgery. RNAlater sample will not be collected in China. Processing of the remainder of the specimens for histopathologic analysis should be performed within 72 hours of the procedure. Sections will be used for central pathology review assessing pathologic complete response (pCR) and major pathological response (MPR). Any tumor, tumor bed, or lymph node specimens that are reviewed locally must be submitted for central pathology review. Gross examination on the entire specimen should be performed which includes all tumor, associated lymph node tissue, and uninvolved parenchyma. The specimen should be sectioned at 0.5 cm intervals, and blocks should be submitted for the full cross section for every other 0.5 cm interval. For very large tumors with no gross evidence of response, a minimum of 1 slide/cm is required for assessment of pathologic response. When estimating viable tumor, in situ carcinoma should not be included. Pathology specimen collection and processing guidelines are outlined in the CA209816 Laboratory Manual. A blinded pathology review process will be utilized to assess for confirmation of endpoints.

Independent Radiology Review: Radiologic tumor assessments will be sent to and reviewed by a Blinded Independent Central Review (BICR) from a third-party radiology vendor on an on-going basis. At the time of investigator assessed radiographic progression per RECIST 1.1, the site must request a BICR- review confirmation of progression or recurrence. However, BICR confirmation of progression should not be requested if investigator judges the progression does not preclude

surgery. Participants should proceed to definitive surgery and tumor assessments post surgery should be continued per schedule of activities. Details of the Blinded Independent Central Review responsibilities and procedures will be specified in the Blinded Independent Central Review charter.

Participants whose disease progression or recurrence is not confirmed by central review will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, even after the initiation of subsequent anti-cancer therapies. Subsequent tumor assessments must be submitted to the third party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the participant to have met RECIST 1.1 criteria for progression or recurrence.

5.2 Number of Participants

Approximately 350 participants will be randomized in a 1:1 ratio (175 participants in each arm) to the 2 arms (neoadjuvant nivolumab plus platinum doublet chemotherapy and platinum doublet chemotherapy), from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03.

In addition, it is expected to have around 70 participants randomized in the original 2-arm study (Arm A and Arm B) and approximately another 75 participants randomized in the arm of neoadjuvant nivolumab plus ipilimumab (Arm A) when the study had 3 arms.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. The analysis of pCR rate will take place after 350 participants on Arms B and C from 1:1:1 randomization defined by revised protocol 02, and 1:1 randomization by revised protocol 03 have the opportunity for surgery. After this analysis, participants will be followed for EFS and OS. Two formal interim analyses for EFS are planned after 148 events and 167 events have been observed in the participants on Arms B and C, which is projected to occur approximately 48 and 58 months after 1:1:1 randomization (the second interim analysis will take place when 167 events are observed [REDACTED]). These formal comparisons of EFS will allow for determination of superiority. The final analysis (FA) of EFS will be conducted after approximately 185 participants in Arms B and C have experienced an event (approximately 73 months from 1:1:1 randomization), or 4 years after the last participant's randomization. [REDACTED]

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Open-Label Design

This study will use an open-label design. Due to the obvious difference in chemotherapy- and immunotherapy-related toxicities, histology-dependent chemotherapy options, different dose modification rules for safety management, including different dose delay rules per arm, and different premedication requirements according to chemotherapy, an open-label design is

appropriate. An open-label design will also help ensure that immune-related toxicities in participant receiving immunotherapy are promptly identified and managed.

Because this study will be open-label, independent pathology and radiology review will be used for central review and confirmation of pathologic and clinical responses in all randomized participants to determine all response-related endpoints.

5.4.2 Rationale for Preoperative Systemic Therapy in NSCLC

Follow-up of adjuvant trials may require decades until a new treatment can be introduced into the early treatment setting. Preoperative chemotherapy has been assessed in a number of trials for patients with resectable NSCLC, though most trials were closed early when the adjuvant chemotherapy data revealed a survival advantage. A meta-analysis based upon 7 trials involving 988 participants suggested that neoadjuvant chemotherapy improved OS when given preoperatively (5-year survival 20% vs 14% without neoadjuvant chemotherapy). This improvement in survival is similar to that noted in the meta-analyses of predominantly adjuvant chemotherapy.^{31,32}

Several studies have shown preoperative cytotoxic chemotherapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity, and mortality.^{6,33,34} Immune checkpoint inhibition has the potential to provide benefits in early-stage disease. Among these benefits are the opportunity to evaluate EFS in a moderate-sized population of early-stage NSCLC patients and the potential to demonstrate long-term, disease-free status in these patients.^{7,35,36,37}

5.4.3 Rationale for Immuno-oncology Treatment in Neoadjuvant NSCLC

In contrast to the adjuvant setting in which only micrometastatic disease is present, one may hypothesize that the higher tumor burden present at the time of induction treatment may be necessary for abundant antigen release and presentation to the immune system, and consequently, development of a robust immune response to immune checkpoint inhibitors.

In an ongoing feasibility trial with nivolumab monotherapy, a major pathologic response (MPR) rate was observed in 45% (9/20) of stage IB-IIIa NSCLC participants who were evaluable post-surgery after 2 cycles of nivolumab. Two patients (10%, 2/20) achieved a pathologic complete response. Major pathologic response was defined as $\leq 10\%$ residual viable tumor at resection.³⁸ Responses were observed across histology and regardless of PD-L1 expression. High tumor mutation burden and neoantigen density was associated with pathological response following neoadjuvant nivolumab treatment. With a median post-op follow-up of 12 months (range of 0.8 to 19.7 months), 1 patient with MPR had a mediastinal lymph-node recurrence that was treated with concurrent chemoradiation and was free from further progression at more than 12 months of follow-up. Two patients without MPR have recurrence of lung cancer (1 solitary brain metastasis which was treated with radiotherapy and has no evidence of further recurrence at more than 16 months of follow-up; 1 systemic recurrence 1 year after surgery and died from recurrent disease 4 months later). Two additional deaths were reported including 1 disease progression in an unresected patient and 1 death not related to drug or disease).

Nivolumab was well tolerated with a safety profile comparable to that observed in the phase 3 program. Administration of nivolumab in the neoadjuvant setting was deemed to be feasible with no surgical delays or post-surgical complications (within 30 days post-surgery). This trial was recently expanded to include an additional 30 participants, who will be treated with nivolumab monotherapy (n=15) and nivolumab plus ipilimumab (n=15). In addition, nivolumab monotherapy will be extended to 3 cycles. It is hypothesized that the addition of a single dose of ipilimumab to 3 doses of nivolumab and the addition of chemotherapy to nivolumab will result in the achievement of higher rate and deeper pathologic responses while maintaining an acceptable safety profile.

The 45% MPR rate from nivolumab in neoadjuvant NSCLC compares with a rate of approximately 20% from platinum doublet chemotherapy in this context. The pCR of 10% also compares favorably to the historically observed pCR rate of approximately 4% with platinum doublet chemotherapy.

In another ongoing phase 2 trial, patients with resectable stage IIIA N2 NSCLC receive 3 cycles of neoadjuvant therapy consisting of nivolumab 360mg IV plus paclitaxel/carboplatin IV Q3W then proceed to definitive surgery after which patients receive 1 year adjuvant nivolumab.³⁹ In the first 22 patients in whom surgical resection was performed following neoadjuvant therapy, pCR was recorded in 13 patients (60%), MPR was noted in a further 4 patients (18%). Neoadjuvant nivolumab plus paclitaxel/carboplatin was well tolerated and surgery was not delayed.

These findings, coupled with encouraging survival data from nivolumab plus ipilimumab and anti-PD1 plus chemotherapy in first-line advanced NSCLC suggest that nivolumab plus ipilimumab, especially nivolumab plus platinum doublet chemotherapy, may improve both EFS and pathologic response relative to platinum doublet chemotherapy, while providing an acceptable safety profile in the neoadjuvant treatment of NSCLC.²⁷

5.4.3.1 Rationale for Combination of Nivolumab and Ipilimumab (Arm A):

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms, to limit T-cell activation. Preliminary indirect data from peripheral T-cell assessments suggests that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity.

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN- γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.⁴⁰

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a phase 1b, multiple ascending dose study in participants with treatment-naïve and previously-treated advanced melanoma. Results showed promising activity with higher but tolerable toxicity than ipilimumab alone. Based on these data, CA209069, a phase 2 study, compared the combination to ipilimumab alone in treatment-naïve participants with advanced melanoma: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks for 4 doses.⁴¹ In participants with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) CRs in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR = 0.4). Recently, a phase 3 study (CA209067, n = 945) reported significantly improved PFS and ORR with the combination of nivolumab and ipilimumab versus ipilimumab alone in previously untreated melanoma. The median PFS was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab plus ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer PFS was observed in the nivolumab plus ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P < 0.001) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; P < 0.001). The hazard ratio for the comparison between the nivolumab plus ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92).⁴²

In addition, deep and durable responses were observed in previously treated, extensive stage small cell lung cancer (SCLC), with a response rate of 31.1% with the combination of nivolumab and ipilimumab.⁴³

Based on the initial data in melanoma and the activity observed with nivolumab and ipilimumab in lung cancer, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in participants with advanced NSCLC. In CA209012, early combination cohorts evaluated 2 dosing schedules that were studied in the CA209004 study in melanoma.⁴⁴

- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg, every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg q 2 weeks (Arms G and H, n=24);
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg, every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg q 2 weeks (Arms I and J, n=25)

These regimens resulted in significant toxicity, with 39% of participants discontinuing treatment due to a treatment-related adverse event. Thus, additional combination cohorts were initiated (Arms N, O, P, Q), using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab with less frequent dosing of ipilimumab. These new regimens were better tolerated, and the safety data are not dissimilar to what has been observed in the nivolumab monotherapy cohort (Arm F in CA209012) (Table 5.4.3.1-1).

Table 5.4.3.1-1: Treatment-related Adverse Events from Selected Cohorts in CA209012

Arm ^a	No. Participants/ arm	Follow-up time (median, wks)	No. Participants still on treatment	No. Participants with drug-related AEs	No. Participants with grade 3-4 drug-related AEs	No. participants d/c due to drug-related AEs (all grades)
N ^b	31	72	6 (19%)	24 (77%)	9 (29%)	4 (13%)
O ^b	40	27	14 (35%)	29 (73%)	14 (35%)	3 (8%)
P ^b	38	37	20 (53%)	28 (74%)	11 (29%)	2 (5%)
Q ^b	39	34	15 (39%)	27 (69%)	11 (28%)	4 (10%)
F ^c	52	62	5 (10%)	37 (71%)	10 (19%)	5 (10%)

^a N: nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks; O: nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; P: nivolumab 3 mg/kg every 2 weeks plus ipilimumab every 12 weeks; Q: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; F: nivolumab 3 mg/kg every 2 weeks

^b based on August 2015 database lock

^c based on March 2015 database lock

Recently, the pooled results from the CA209012 (Checkmate 012) nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q12W and Q6W cohorts showed continued clinical benefit (OS and PFS) with nivolumab plus ipilimumab in all patients and those with $\geq 1\%$ and $\geq 50\%$ tumor PD-L1 expression.⁴⁵ ORR was 43% in all treated patients and 57% and 92% in patients with $\geq 1\%$ and $\geq 50\%$ tumor PD-L1 expression, respectively, consistent with the previous report. Additionally, 6 investigator-assessed complete responses ([CRs] 8%; including 3 pathologic responses) were achieved in the Q12W/Q6W cohorts.⁴⁶ Median duration of response had not yet been reached in the overall population or in subgroups with $<1\%$, $\geq 1\%$, or $\geq 50\%$ PD-L1 expression; duration of response ranged from 1.4+ to 27.9+ months. All treated patients (n = 77) showed a 1 year OS of 76% and 2 year OS of 49%. When analyzed by PD-L1 expression, patients with $\geq 1\%$ PD-L1 (n = 47) had a 1 year OS of 87% and 2 year OS of 58%, which increased to 100% and 62%, respectively for $\geq 50\%$ PD-L1 patients. Nivolumab plus ipilimumab remained tolerable, as most treatment-related AEs were manageable and no new safety concerns were identified in follow-up. As described in Section 3.2.1, ongoing phase 3 CheckMate 227 study randomized patients with stage IV or recurrent NSCLC that was not previously treated in various study treatment arms by tumor PD-L1 status. Recently, in the pre-specified analysis of patients with high tumor mutational burden at a prospective cutoff of ≥ 10 mutations/MB, progression-free survival was significantly longer in the group treated by nivolumab plus ipilimumab compared to chemotherapy, HR of PFS being 0.58 (97.5% CI 0.41, 0.81). The treatment effect was consistent and independent of PD-L1

expression or histology. The ORR was also significantly greater for the nivolumab plus ipilimumab group (45.3% vs 26.9%) and the responses appeared more durable with median DoR not reached (95% CI 12.2, NR) compared to 5.4 months (95% CI 4.2, 6.9) for chemotherapy. In patients with TMB < 10 mut/Mb, similar efficacy was seen in terms of PFS and ORR between nivolumab plus ipilimumab and chemotherapy. The safety profile was overall consistent with previously reported data with no new safety signals. In another readout focusing on patients with tumor of <1% PD-L1 expression, nivolumab plus ipilimumab showed similar efficacy to chemotherapy in terms of PFS and ORR but with much longer DoR, the safety profile was consistent with previously reported data.

5.4.3.2 Rationale for PD-1 Inhibitor with Chemotherapy (Arm C)

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

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

Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012. Nivolumab 10 mg/kg was combined with gemcitabine and cisplatin and pemetrexed + cisplatin. Nivolumab 10 mg/kg and 5 mg/kg was combined with paclitaxel and carboplatin.

The safety profile of nivolumab plus platinum-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 subjects (13%): Grade 3-4 in 4 subjects (7%). Twelve (21%) subjects discontinued due to treatment-related AEs (Table 5.4.3.2-1).

The overall response rate across all the nivolumab and chemotherapy cohorts ranged from 33-47% and median duration of response was 27.3 weeks. In the 15 participants that received nivolumab 10 mg/kg plus pemetrexed and cisplatin, 47% achieved a PR or CR. In the 12 participants that received nivolumab 10 mg/kg plus gemcitabine and cisplatin, 33% achieved a CR or PR. The 1-year survival rate was 87% (Table 5.4.3.2-2).

Activity was evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors. Overall, 79% (44/56) of subjects had evaluable tumor samples. At the $\geq 1\%$ 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 5.4.3.2-1: Safety Evaluation in CA209012

	Total (N=56)		
	All Grades	Grade 3	Grade 4
Subjects 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
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).

Table 5.4.3.2-2: Efficacy of First-Line Treatment of Nivolumab/Chemotherapy Combination in CA209012

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	27.3	27.3
12-mo OS rate, %	50	87	72	86
18-mo OS Rate, %	33	60	40	62
Median OS, Weeks	51	83	65	Not Reached

As described in [Section 3.2.1](#), 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]), mPFS of nivolumab plus ipilimumab was 4.4 months (95%CI: 3.1 to 6.0). ORR was 36.7% in nivolumab plus chemotherapy arm, 23.1% in chemotherapy arm, and 25.1% in nivolumab plus ipilimumab arm. mDOR was 7.2 months in nivolumab plus chemotherapy arm, 4.7 months in chemotherapy arm, and 18.0 months in nivolumab plus ipilimumab arm. The rate of grade 3 or 4 treatment-related adverse events was 52% with nivolumab plus chemotherapy, 35% with chemotherapy, and 25% with nivolumab plus ipilimumab, overall, for nivolumab plus chemotherapy, the safety profile and efficacy are consistent with previously reported data as well as data from other PD-(L)1 blockades in combination with chemotherapy.

5.4.4 Rationale for Pathologic Response

Pathologic complete response (pCR) has been long known to correlate with survival after tumor resection. Recently, the FDA approved pertuzumab based on pathologic response rate for the treatment of locally advanced breast cancer. In the ongoing feasibility trial with nivolumab monotherapy, 2 out of 20 (10%) patients achieved pCR. In another ongoing phase II trial (NADIM) to evaluate neoadjuvant nivolumab plus chemotherapy, 13 out of 22 (60%) patients achieved pCR. These compare favorably to the approximate 4% pCR in NSCLC observed historically with neoadjuvant chemotherapy. It is predicted that patients treated with the combination of nivolumab plus ipilimumab, especially nivolumab plus platinum doublet chemotherapy, will achieve a higher pCR rate than in patients treated with nivolumab monotherapy. Therefore, pCR will be one of primary objectives.

In a recent publication by Hellmann and colleagues, major pathologic response (MPR), defined as ≤10% viable tumor, was proposed as a better surrogate for survival and is observed in

approximately 22% of NSCLC patients treated with neoadjuvant chemotherapy.⁴⁷ This proposed surrogate for survival was supported by the data from a prospective study and retrospective study.^{48,49} Pataer and colleagues used a score system that quantifies the percentage of viable tumor cells and demonstrated that there is a statistically significant correlation between higher percentage of viable cells and shorter disease-free and OS in patients who received induction treatment. This correlation was not evident in patients treated with upfront surgery alone. The 5-year recurrence-free survival for patients with and without a pathologic response were 78% and 35%, respectively ($P < 0.001$). The 5-year overall survival for patients with and without a pathologic response were 85% and 40%, respectively ($P < 0.0001$). In the on-going feasibility CA209159 trial with nivolumab monotherapy, a MPR rate of 45% (9/20) was observed in stage IB-IIIa NSCLC participants who were evaluable post-surgery after 2 cycles of nivolumab. In NADIM, further to 60% pCR rate, MPR was also noted in 4 additional patients (18%). These results compare favorably to the MPR rate of approximately 22% observed with historical neoadjuvant chemotherapy. These results further support the exploration of MPR as a secondary objective for the CA209816 trial.

5.4.5 Rationale for Patient Population

The OS benefit of several adjuvant therapies in this population is presented in Table 3.1-1. The choice of stage II and resectable IIIa (N2) NSCLC was made because these participants have a high risk of tumor relapse and death with current standard therapy, including surgery with preoperative or postoperative chemotherapy. There is an urgent need for improved, novel therapies for this group of participants. Participants with stage IB NSCLC with primary tumors of ≥ 4 cm diameter have been included because these participants are also at a high risk of tumor relapse and may be considered candidates for standard adjuvant chemotherapy.^{2,50} It is anticipated that participants enrolled on this study may require adjuvant chemotherapy with or without radiation, and the administration of adjuvant chemotherapy will commence if considered clinically indicated in the postoperative period.

5.4.6 Rationale for Choices of Platinum-based Chemotherapy Doublet

The regimens selected for use in this study are commonly used adjuvant and neoadjuvant therapies in the clinical setting. A significant difference in outcome was not seen between participants using the regimens proposed in this trial.⁵¹ Cisplatin-based therapy has been shown to significantly improve survival.⁵² Several clinical trials have found a significant improvement in OS when using platinum-based chemotherapy regimens.^{53,54,55,56,57} In revised protocol 03, paclitaxel/carboplatin is added among available chemotherapy options based on the promising data of using this doublet as backbone to combine with nivolumab in neoadjuvant therapy. Besides, meta-analysis of individual participant data from neoadjuvant trials did not identify evidence of a difference in effect of chemotherapy by whether regimens were cisplatin or carboplatin-based (interaction $p=0.48$).⁵⁸

5.5 Justification for Dose

5.5.1 Rationale for Shorter Infusion Times for Nivolumab

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010 (a phase 2, randomized, double-blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg of nivolumab and for a flat dose of 360 mg (30% of the dose provided at 10 mg/kg and 45% of dose provided at 10 mg/kg assuming an average body weight of 80 kg, respectively) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

Of note, CA209153, a phase 3b/4 safety study of nivolumab in participants with metastatic NSCLC who have progressed during or after at least 1 prior systemic regimen, used a 30-minute infusion in a cohort of participants with no safety issues.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab.

5.5.2 Rationale for Nivolumab 360 mg Flat 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 subjects 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 subjects.

A PPK model predicted overall nivolumab exposures across subjects 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.

In addition, data from the Japanese Phase 1 study ONO-4538-01 did not demonstrate dose-limiting toxicity at nivolumab up to 20 mg/kg every 2 weeks in Japanese patients and showed similarity in

PK properties between Global and Japanese population. Therefore, the proposed 360 mg flat dose is expected to be safe and tolerable in an Asian population.

Nivolumab 5 or 10 mg 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 CA209722.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

- a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.
- b) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2) Type of Participant and Target Disease Characteristics

- a) Eastern Cooperative Group (ECOG) Performance Status 0-1 ([Appendix 3](#))
- b) Participants with histologically confirmed Stage IB (≥ 4 cm), II, IIIA (N2) NSCLC (per the 7th International Association for the Study of Lung Cancer) with disease that is considered resectable.⁵⁹
- c) Measurable disease according to RECIST version 1.1
- d) Participants must have a tumor tissue sample available for PD-L1 IHC testing performed by a third-party analyzing lab during the screening period:
 - i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The tumor tissue sample may be fresh or archival if obtained within 3 months prior to enrollment.
 - ii) Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies obtained by EBUS is not considered adequate for biomarker review and randomization. Core needle biopsies obtained by EBUS are acceptable for randomization.
- e) Absence of major associated pathologies that increase the surgery risk to an unacceptable level
- f) All suspicious mediastinal lymph nodes including those that are pathologically enlarged or FDG avid on PET/CT require further sampling for pathological confirmation if accessible by mediastinoscopy, thoracoscopy, or EBUS.
- g) Pulmonary function capacity (eg, FVC, FEV1, TLC, FRC, and DLco) capable of tolerating the proposed lung resection according to the surgeon.

3) Age and Reproductive Status

- a) Males and Females, ages ≥ 18 or age of majority
- 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) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (Appendix 6) for the duration of treatment with nivolumab and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately 5 half-lives (for participants treated in Arm A and Arm C).
- e) WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for participants treated in Arm B and Arm C).
- f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 6) for the duration of treatment with nivolumab and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately 5 half-lives) (for participants treated in Arm A and Arm C). In addition, male participants must be willing to refrain from sperm donation during this time.
- g) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) with chemotherapy plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (participants in Arm B and Arm C). In addition, male participants must be willing to refrain from sperm donation during this time.
- h) 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 6), which have a failure rate of $< 1\%$ when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

- a) Presence of locally advanced unresectable (regardless of stage) or metastatic disease (stage IV).
- b) Participants with known EGFR mutations or ALK translocation. If testing is done, an FDA-approved assay should be used, and testing will be performed locally.
- c) Participants with brain metastases are excluded from this study, and all participants with stage II or higher disease and those with suspicion of brain metastases should have MRI or CT of the brain with pre- and post-contrast within 28 days prior to randomization.
- d) Participants with \geq Grade 2 peripheral neuropathy
- e) 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.
- f) 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
- g) 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.
- h) Participants with serious or uncontrolled medical disorders
- i) Participants with large-cell neuroendocrine carcinoma tumor histology

2) Prior/Concomitant Therapy

- a) Prior administration of chemotherapy or any other cancer therapy for early stage NSCLC.
- b) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL-2, or anti-CTLA-4 antibody or any other antibody targeting T cell co-regulatory pathways.

3) Physical and Laboratory Test Findings

- a) Screening laboratory values must meet the following criteria (using CTCAE v4):
 - i) WBC $< 2000/\mu\text{L}$
 - ii) Neutrophils $< 1500/\mu\text{L}$
 - iii) Platelets $< 100 \times 10^3/\mu\text{L}$
 - iv) Hemoglobin < 9.0 g/dL
 - v) Serum creatinine > 1.5 x ULN or calculated creatinine clearance (CrCl) < 50 mL/min (using the Cockcroft-Gault formula)
Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$
Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$
 - vi) AST > 3.0 x ULN

- vii) ALT > 3.0 x ULN
 - viii) Total Bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN).
 - b) Participants with active hepatitis B (positive hepatitis B surface antigen [HBsAg] or hepatitis C virus (HCV) (positive HCV RNA)
 - i) Participants with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and the absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to randomization. HBV carriers or those participants requiring antiviral therapy are not eligible to participate.
 - ii) Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
 - c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
 - d) Participants with serious or uncontrolled medical disorders
- 4) Allergies and Adverse Drug Reaction**
- a) History of allergy or hypersensitivity to study drug components
- 5) Other Exclusion Criteria**
- a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb Company 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.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who 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. Participants are allowed to re-enroll twice. Eligibility will need to be confirmed if a participant is re-enrolled.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted up to 3 times (in addition to any parameters that require a confirmatory value).

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

7 TREATMENT

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

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

All products, active or placebo, being tested or used as a comparator in a clinical trial.

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

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

Table 7-1: Study treatments for CA209816

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection/Nivolumab ^a	10 mg/mL	IP	Open-label	5 or 10 (100 mg) vials per carton; Clear to opalescent, colorless to pale yellow liquid. Few particulates may be present.	2 to 8° C. Protect from light and freezing
Ipilimumab Solution for Injection	5 mg/mL	IP	Open-label	4 vials/carton. Clear to opalescent, colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Vinorelbine NC Concentrate for Solution for Infusion ^b	10 mg/mL	IP	Open-label	1 vial/carton. Clear, colorless to pale yellow solution.	Product should be stored as per market product conditions.
Gemcitabine Concentrate for Solution for Infusion ^b	1000 mg/vial (38 mg/mL)	IP	Open-label	1 vial/carton. Clear, colorless or light straw-colored solution	Product should be stored as per market product conditions.
Gemcitabine Powder for Solution for Infusion ^b	1000 mg/vial	IP	Open label	1 vial per carton. White to off-white plug or powder	Product should be stored as per market product conditions.
Docetaxel Concentrate for Solution for Infusion ^b	10 mg/mL	IP	Open-label	1 vial/carton. Pale yellow to brownish yellow 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	1 vial/carton. White to either light yellow or green-yellow lyophilised powder	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	4 vials per carton. Clear, colorless solution	Product should be stored as per market product conditions.

Table 7-1: Study treatments for CA209816

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Carboplatin Solution for Injection ^b	450 mg/vial (10 mg/mL)	IP	Open-label	4 vials/carton. Clear, colorless or slightly yellow solution.	Product should be stored as per market product conditions.
Paclitaxel Solution for Injection ^b	100mg/vial (6mg/mL)	IP	Open-label	4 vials/carton. Clear, colorless or slightly yellow viscous solution.	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 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, stored and administered with the Package Insert or Summary of Product Characteristics.

Note: As of revised protocol 03, enrollment in nivolumab + ipilimumab arm has stopped enrollment.

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

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	10 mg/mL	3 mg/kg every 2 weeks for up to 3 cycles (Arm A) 360 mg every 3 weeks for up to 3 cycles (Arm C)	IV
Ipilimumab	5 mg/mL	1 mg/kg at Cycle 1 only	IV
Vinorelbine ⁶⁰	10 mg/mL	25 mg/m ² or 30 mg/m ² on Days 1 and 8 of a 3-week cycle for up to 3 cycles ^a	IV
Gemcitabine ⁶¹	38 mg/mL	1000 mg/m ² or 1250 mg/m ² on Days 1 and 8 of a 3-week cycle for up to 3 cycles ^a	IV
Docetaxel ⁶²	10 mg/mL	60 mg/m ² or 75 mg/m ² on Day 1 of a 3-week cycle for up to 3 cycles ^a	IV
Pemetrexed ⁶³	500 mg/vial	500 mg/m ² on Day 1 of a 3-week cycle for up to 3 cycles ^a	IV
Cisplatin ⁶⁴	1 mg/mL	75 mg/m ² on Day 1 of a 3-week cycle for up to 3 cycles ^a	IV
Carboplatin ⁶⁵	10 mg/mL	AUC 5 or 6 on Day 1 of a 3-week cycle for up to 3 cycles ^{a,b}	IV.
Paclitaxel (Taxol PI TBC) ^{66,67}	6 mg/mL	175 or 200 mg/m ² on Day 1 of a 3-week cycle for up to 3 cycles ^a	IV

^a Following definitive surgery, participants may receive up to 4 cycles of adjuvant chemotherapy with or without radiation at the discretion of the investigator.

^b Carboplatin is initiated at a dose of AUC 5 or 6 when combined with paclitaxel.

Note: As of revised protocol 03, enrollment in nivolumab + ipilimumab arm has stopped enrollment.

Nivolumab and Ipilimumab (Arm A)

NOTE: As of revised protocol 03, enrollment has stopped in Arm A.

Participants are to receive nivolumab at a dose of 3 mg/kg as a 30-minute infusion on Day 1 of each treatment cycle every 2 weeks for a maximum of 3 doses. In Cycle 1, participants will also receive a single dose of ipilimumab 1 mg/kg as a 30-minute infusion on Day 1. Participants are to begin study treatment within 7 calendar days of randomization.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram or per institutional standard.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Participants may be dosed no less than 12 days from the previous dose. Premedications are not recommended for the first dose of nivolumab and ipilimumab.

Participants should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to [Section 7.4.3](#).

Doses of nivolumab and ipilimumab may be interrupted, delayed, or discontinued depending on how well the participants tolerates the treatment. If a participant requires a dose delay of > 7 days, the dose should be skipped.

Dose delay criteria can be found in [Section 7.4.2.1](#), and discontinuation criteria can be found in [Section 8.1.1.1](#). Criteria to resume treatment can be found in [Section 8.1.2.1](#).

Please see the nivolumab IB, ipilimumab IB, and pharmacy manual for specific infusion preparation recommendations.

Nivolumab plus Platinum Doublet Chemotherapy (Arm C)

Participants are to begin study treatment within 7 calendar days of randomization. Participants are to receive nivolumab 360 mg IV plus histology dependent platinum doublet chemotherapy in 3-week cycles up to a maximum of 3 cycles:

- Non-squamous NSCLC: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by pemetrexed at a dose of 500 mg/m² IV over 10 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, of a 3-week treatment cycle, for up to 3 cycles.
- Squamous NSCLC: nivolumab at a flat dose of 360 mg as 30 minute IV infusion on day 1, followed by gemcitabine at a dose of 1000 mg/m² or 1250 mg/m² (per local prescribing information) IV over 30 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, of a 3-week treatment cycle for up to 3 cycles. Gemcitabine will also be administered at a dose of 1000 mg/m² or 1250 mg/m² for a 30 minute IV infusion or per institutional standard on day 8 of each 3-week treatment cycle.

- Any histology: nivolumab at a flat dose of 360 mg as 30-minute IV infusion on Day 1, followed by paclitaxel 175 or 200 mg/m² IV over 180 minutes or per institutional standard and carboplatin AUC 5 or 6 IV over 30 minutes or per institutional standard of a 3-week treatment cycle, for up to 3 cycles.
- 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.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 18 days from the previous dose. 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 tolerate the treatment. If a participant requires a dose delay of > 7 days, the dose should be skipped.

Dose delay criteria can be found in [Section 7.4.2.1](#), and discontinuation criteria can be found in [Section 8.1.1.1](#). Criteria to resume treatment can be found in [Section 8.1.2.1](#).

Please see the nivolumab IB, ipilimumab IB, and pharmacy manual for specific infusion preparation recommendations.

Refer to instructions below for instructions for pemetrexed/cisplatin, gemcitabine/cisplatin, and paclitaxel/carboplatin administration.

Doses of gemcitabine and/or cisplatin 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 8.1.1.2](#). Criteria to resume treatment can be found in [Section 8.1.2.2](#).

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 8.1.1.2](#). 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.

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 8.1.1.2](#). Criteria to resume treatment can be found in [Section 8.1.2.2](#).

Dosing of all drugs should be delayed if any criteria in [Section 7.4.2.1](#) (nivolumab), [Section 7.4.2.2](#), or [Section 7.4.2.3](#) (platinum doublet chemotherapy) are met. That is, nivolumab should be delayed if criteria for delay of platinum doublet chemotherapy are met, and platinum doublet chemotherapy should be delayed if criteria for delay of nivolumab are met.

Participants may resume dosing only when criteria for BOTH resumption of nivolumab ([Section 8.1.2.1](#)) AND platinum doublet chemotherapy ([Section 8.1.2.2](#) and [Section 8.1.2.3](#)) are met. That is, nivolumab and platinum doublet chemotherapy must be administered together until treatment discontinuation criteria ([Sections 8.1.1.1](#), [8.1.1.2](#), and [8.1.1.3](#)) or up to 3 cycles of study treatment have been completed.

If a participant who is receiving nivolumab and platinum doublet chemotherapy experiences an adverse event and the investigator can attribute it to either nivolumab or chemotherapy, then either nivolumab or the chemotherapy agents can be discontinued, and the other agent(s) can be continued.

Platinum Doublet Chemotherapy (Arm B)

Vinorelbine/Cisplatin

Vinorelbine will be administered at a dose of 25 mg/m² or 30 mg/m² (per local prescribing information) over 10 minutes or per institutional standard as an IV infusion on Days 1 and 8 followed by cisplatin at a dose of 75 mg/m² as a 120-minute or per institutional standard IV infusion on Day 1 only, of a 3-week treatment cycle for up to 3 cycles.

Dosing calculations for vinorelbine 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. Doses of vinorelbine and/or cisplatin may be interrupted, delayed, reduced, 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 8.1.1.2](#). Criteria to resume treatment can be found in [Section 8.1.2.2](#).

See below for the details regarding administration of cisplatin.

Docetaxel/Cisplatin

Docetaxel will be administered at a dose of 60 mg/m² or 75 mg/m² (per local prescribing information) as a 60 minute or per institutional standard IV infusion on Day 1 followed by cisplatin

at a dose of 75 mg/m² as a 120 minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 3 cycles.

Dosing calculations for docetaxel 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. Dose modifications for toxicity will be performed according to [Section 7.4.1](#). Dose delay criteria can be found in [Section 7.4.2.3](#), and dose discontinuation criteria can be found in [Section 8.1.1.3](#). Criteria to resume treatment can be found in [Section 8.1.2.3](#).

See below for the details regarding administration of cisplatin.

Premedications for use with docetaxel: Premedication with corticosteroids will be given to participants receiving docetaxel. The recommended premedication per the USPI and SmPC is dexamethasone 8 mg PO twice daily given one day before, on the day of, and one day after administration of chemotherapy. For institutions that have established an equivalent premedication regimen consistent with local docetaxel labeling, such premedication regimens will be permitted.

Gemcitabine/Cisplatin (Squamous histology only)

Participants will receive gemcitabine at a dose of 1000 mg/m² or 1250 mg/m² (per local prescribing information) as a 30 minute or per local institutional standard IV infusion on Days 1 and 8 followed by cisplatin at a dose of 75 mg/m² as a 120-minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 3 cycles. Prolonged gemcitabine infusions > 60 minutes and/or administration more frequent than weekly has been associated with increased toxicity.

Dosing calculations for gemcitabine 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.

Doses of gemcitabine and/or cisplatin 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 8.1.1.2](#). Criteria to resume treatment can be found in [Section 8.1.2.2](#).

See below for the details regarding administration of cisplatin.

Pemetrexed/Cisplatin (non-Squamous histology only)

Pemetrexed will be administered at a dose of 500 mg/m² as a 10 minute or per institutional standard IV infusion and cisplatin will be administered at a dose of 75 mg/m² as a 120-minute or per institutional standard IV infusion on Day 1 of a 3-week treatment cycle for up to 3 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.

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 8.1.1.2](#). 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.

See below for the details regarding administration of cisplatin.

Paclitaxel/Carboplatin

Paclitaxel will be administered at a dose of 175 or 200 mg/m² 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 3 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.

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 8.1.1.2](#). Criteria to resume treatment can be found in [Section 8.1.2.2](#).

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.

Cisplatin

Cisplatin 75 mg/m² as a 120 minute or per institutional standard IV infusion will be administered to participants as the second infusion. Dosing calculations for cisplatin 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.

Pretreatment hydration for cisplatin can follow local standard of care or use 1 to 2 liters of fluid 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.

All participants who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, as per local or institutional standards of care. Participants considered to be at higher risk for ototoxicity with cisplatin have the option to receive carboplatin-based chemotherapy regimen after discussion with the Medical Monitor.

For participants who are unable to tolerate cisplatin, the reasons for intolerability should be documented. If the investigator would like to use a carboplatin-based regimen, the investigator should discuss this with and obtain approval from the Medical Monitor prior to utilization, except for opting for carboplatin plus paclitaxel.

Carboplatin

Carboplatin will be administered at a dose of AUC 5 or 6 as a 30-minute or as per institutional standard IV infusion, on Day 1 of each 3-week cycle.

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

- Carboplatin dose (mg) will be calculated using the Calvert formula as follows = 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.

For All Arms Containing Chemotherapy:

Participants should begin study treatment within 7 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 later than 7 days following a planned dose on any arm.

If more than 7 days delay is needed for any reason, the intended dose should be skipped. If a participant receiving chemotherapy on a Day 1 and Day 8 schedule (ie, cisplatin/gemcitabine) is unable to receive Day 1 of chemotherapy but recovers in time to receive the Day 8 dose, the Day 8 dose of chemotherapy may be administered.

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.

7.2 Method of Treatment Assignment

CA209816 is an open-label, randomized trial. Participants with Stage IB (≥ 4 cm), II and IIIA (N2) considered resectable will be eligible to participate. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling the IRT to obtain a participant number. Every participant that signs the informed consent form must be assigned a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth, where applicable by local regulations
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through IRT. PD-L1 expression data will be transferred directly from analyzing lab to IRT. The following information is required for participant randomization:

- Participant number
- Date of birth, where applicable per local regulations
- Stage of disease (IB, IIA, IIB or IIIA)
- PD-L1 status
- Gender

Participants meeting all eligibility criteria will be stratified according to PD-L1 status into 2 categories ($\geq 1\%$ and $< 1\%$ or not evaluable/indeterminate). Enrollment of participants with not evaluable or indeterminate PD-L1 status will be capped at 10%. Participants will also be stratified based disease stage (IB/II vs IIIA) and gender.

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

7.3 Blinding

This is an open-label study; blinding procedures between participants and investigators are not applicable. The BIPR and BICR will be blinded.

7.4 Dosage Modification

7.4.1 Dose Reductions for Platinum Doublet Chemotherapy

Dose reductions of platinum 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 doublet chemotherapy regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.1-1: Dose Modifications of Chemotherapeutic Agents^a

Dose Level	Vinorelbine	Docetaxel	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Starting dose	25mg/m ² or 30 mg/m ²	60 mg/mg ² or 75 mg/m ²	1000 mg/m ² or 1250 mg/m ²	500 mg/m ²	75 mg/m ²	AUC 5 or 6	175 or 200 mg/m ²
First dose reduction	75% of starting dose	75% of starting dose	75% of starting dose	75% of starting dose	75% of starting dose	AUC 4 or 5	150 mg/m ²
Second dose reduction	50% of the starting dose	50% of starting dose	50% of the starting dose	50% of the starting dose	50% of the starting dose	AUC 3 or 4	100 mg/m ²
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

^a Follow local regulations if they are different than what appears in this table.

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

7.4.1.1 Platinum 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 doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the platinum doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

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

Toxicity	Vinorelbine	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Neutrophil Count Decreased						
Grade 4 ($< 500/\text{mm}^3$ or $< 0.5 \times 10^9/\text{L}$)	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles
Platelet Count Decreased						
Grade 3 ($25,000$ to $< 50,000/\text{mm}^3$; 25.0 to $< 50.0 \times 10^9/\text{L}$)	Reduce one dose level					
Grade 4 ($< 25,000/\text{mm}^3$; $< 25.0 \times 10^9/\text{L}$)	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					
Grade 3 (< 8.0 g/dL; < 4.9 mmol/L, < 80 g/L)	Reduce one dose level					
Grade 4 (Life threatening consequences)	Hold drug					

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

Dose Modifications for Hematologic Toxicity for Docetaxel: Doses of docetaxel will be modified for participants who experience docetaxel-related events of febrile neutropenia, neutrophils < 500 cell/mm³ for > 7 days during docetaxel treatment. Participants should have treatment delayed according to [Section 7.4.2.3](#) and then resumed at 1 dose level reduction (75% of starting dose). Should these AEs occur after the first dose reduction, then a second dose reduction to (50% of starting dose) is permitted. If a third dose reduction is required, then the participants should discontinue docetaxel treatment.

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

Dose adjustments for platinum doublet chemotherapy for non-hematologic toxicities during treatment are described in [Table 7.4.1.2-1](#). All dose reductions should be made based on the worst grade toxicity. Participants experiencing any of the toxicities detailed in [Table 7.4.1.2-1](#) during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per [Section 8.1.2.2](#)) and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the platinum-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^{a,b}

Toxicity	Vinorelbine	Gemcitabine	Pemetrexed	Cisplatin	Carboplatin	Paclitaxel
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	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	Reduce one dose level	Reduce one dose level	No change	No change	Reduce one dose level
Allergic reaction^c Grade ≥ 3	Reduce one dose level	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No Change	No change	No change	Reduce one dose level ^d	No change	Reduce one dose level
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	No change	No change	Discontinue if creatinine clearance < 45 mL/min	Discontinue	Discontinue if creatinine clearance < 20 mL/min	No change
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	Adjust as medically indicated

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

^b Please see local drug label for additional adjustments.

^c Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (\geq Grade 3) require(s) discontinuation. All other drugs may be continued.

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

Participants receiving docetaxel who develop Grade ≥ 3 peripheral neuropathy, or who otherwise meet criteria specified in [Section 8.1.1.3](#), should discontinue docetaxel treatment.

Dose Modifications for Non-hematologic Toxicity for Docetaxel: Doses of docetaxel will be modified for participants who experience docetaxel-related events of severe or cumulative cutaneous reactions or other Grade 3/4 non-hematological toxicities during docetaxel treatment. Participants should have treatment delayed according to [Section 7.4.2.3](#) and then resumed at 1 dose level reduction (75% of starting dose). Should these AEs occur after the first dose reduction, then a second dose reduction to (50% of starting dose) is permitted. If a third dose reduction is required, then the participants should discontinue docetaxel treatment.

7.4.2 Dose Delay

If any agent is delayed > 7 days, the dose should be skipped, and the participant should resume treatment at the next scheduled dose if criteria to resume treatment ([Section 8.1.2](#)) for the appropriate arm are met. If the last dose of study drug is delayed >7 but < 11 days, while it is recommended that this dose be skipped, if the investigator feels that it is appropriate to administer the last dose, discuss with the Medical Monitor before administering the last dose of study drug.

7.4.2.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- 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 8.1.1.1](#))
- 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 Doublet Chemotherapy

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

- Absolute neutrophil count (ANC) $\leq 1500/\mu\text{L}$
- Platelets $< 100,000/\text{mm}^3$
- 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.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays. Participants receiving gemcitabine with cisplatin or carboplatin should omit the Day 8 gemcitabine dose for any of the following on Day 8 of any cycle:

- ANC $< 1,000/\text{mm}^3$
- Platelets $< 75,000/\text{mm}^3$

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 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 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 8.1.2.2](#) or [Section 8.1.2.3](#)).

7.4.2.3 Docetaxel Dose Delay Criteria

Docetaxel administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
 - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, neutrophil count, AST, ALT, or total bilirubin:
 - Grade 3 lymphopenia does not require dose delay
 - Should not be given if neutrophil counts are $< 1500 \text{ cells}/\text{mm}^3$
 - Should not be given if total bilirubin $>$ upper limit of normal (ULN), or if AST and/or ALT $> 1.5 \times \text{ULN}$ concomitant with alkaline phosphatase $> 2.5 \times \text{ULN}$

- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Subsequent dose reductions may be required as per [Section 7.4.1](#).

Participants receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

7.4.3 Treatment of Nivolumab- and Ipilimumab-related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI 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 required 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/ipilimumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- 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 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone 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/ipilimumab. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

Handling of chemotherapy should be according to local prescribing information.

Please refer to the current version of the Investigator Brochures (IBs) and/or the Pharmacy Manual for complete storage, handling, and preparation information. Further guidance and information for final disposition of unused study treatment are provided in [Appendix 7](#) and the Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

At the time of receipt of the investigational product by the investigator or designee's, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of

the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper evident seal provided by BMS. Package labeling should clearly identify the contents as bioavailability/bioequivalence (BA/BE) samples and state that the investigational product should be stored in the restricted area with limited access.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

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 7.7.3](#))
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Investigators should refer to the local product labeling for the chemotherapy drugs selected for use in Arm B and Arm C and for additional prohibited and restricted concomitant medications.
- Caution should be used regarding the use of herbal medication, as there may be as yet unknown interactions with nivolumab and ipilimumab. Discontinuation of the use of herbal medications prior to the study enrollment is encouraged.
- Live vaccines (eg, yellow fever, MMR, nasal flu vaccine, chicken pox [varicella]) should be avoided while receiving neoadjuvant or adjuvant study drug
- Avoid using concomitant strong CYP3A4 inhibitors or inducers with docetaxel, vinorelbine, or paclitaxel. Avoid using concomitant strong CYP2C8 inhibitors or inducers with paclitaxel. Consult the local prescribing information for further guidance.
- Avoid the concomitant administration of substances that are also tubularly secreted (eg, probenecid) which could potentially result in delayed clearance of pemetrexed.

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.

It is the local imaging facility's responsibility to determine, based on participants attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

7.7.3 Permitted Therapy

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

7.8 Treatment After the End of the Study

At the end of the study period, 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 lung cancer treatment.

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. Participant should notify the investigator of the decision to withdraw from future follow-up in writing, whenever possible, and this should be documented in the medical records.
- 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 Company (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

Refer to the Schedule of Activities for data to be collected at the time of neoadjuvant treatment discontinuation and subsequent study procedures and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant

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

All participants who discontinue study treatment should comply with protocol specified 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.

8.1.1 Study Treatment Discontinuation Criteria

Doses that are missed or delayed by > 7 days will not be replaced, and participants should proceed to surgery within the indicated timelines. Participants who discontinue their assigned study treatment prematurely will not be allowed to receive subsequent neoadjuvant therapy, and participants should proceed to surgery within the indicated timelines.

In Arm C, nivolumab and platinum doublet chemotherapy can be discontinued independently based on their discontinuation criteria.

8.1.1.1 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 adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
 - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
 - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
 - ◆ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
 - ◆ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
 - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
- * In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
 - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality (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 of any study drug for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
 - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

8.1.1.2 Platinum Doublet Chemotherapy Dose Discontinuation

Except where specified below, both chemotherapy drugs in the platinum 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 - 10 x ULN for > 2 weeks
 - AST or ALT > 10 x 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 Cockcroft Gault formula) requires discontinuation of cisplatin. The other chemotherapeutic agent may be continued, and the platinum agent may be switched to carboplatin, 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 Cockcroft 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 > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
 - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued platinum doublet chemotherapy dosing. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.

For participants in Arms C, if the investigator is unable to determine whether an adverse event is due to nivolumab or to platinum doublet chemotherapy, then all drugs must be discontinued.

8.1.1.3 Docetaxel Dose Discontinuation

Docetaxel treatment should be permanently discontinued for the following:

- Any \geq Grade 3 peripheral neuropathy
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities:
 - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except
 - ◆ Grade 3 drug-related thrombocytopenia associated with bleeding requires discontinuation.
 - ◆ Any drug-related liver function test (LFT) abnormalities that meets the following criteria require discontinuation:
 - AST or ALT $> 5 - 10x$ ULN for > 2 weeks
 - AST or ALT $> 10x$ ULN
 - Total bilirubin $> 5x$ ULN
 - Concurrent AST or ALT $> 3x$ ULN and total bilirubin $> 2x$ ULN
- Any Grade 4 drug-related adverse event including laboratory abnormalities except for the following events which do not require discontinuation:
 - Grade 4 neutropenia > 7 days despite 2 prior docetaxel reductions requires discontinuation
 - Grade 4 lymphopenia or leukopenia does not require discontinuation
 - 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 does not require discontinuation.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
 - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/Study Director. Prior to re-initiating treatment in a participant with a dosing interruption lasting > 6 weeks, the BMS Medical Monitor/Study Director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

8.1.2 Criteria to Resume Treatment

8.1.2.1 Criteria to Resume Nivolumab Treatment

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Please refer to the Management Algorithms in Appendix 4.

8.1.2.2 Criteria to Resume Platinum Doublet Chemotherapy Dosing

- Participants may resume treatment with platinum doublet chemotherapy when the ANC returns to $\geq 1500/\mu\text{L}$, the platelet count returns to $\geq 100,000/\text{mm}^3$, 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 reinitiating treatment, then treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated
- When resuming platinum doublet chemotherapy treatment, please follow the dose reduction recommendations in Section 7.4.1

8.1.2.3 Criteria to Resume Treatment with Docetaxel

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Participants with decreased neutrophil counts, or with elevations in total bilirubin, AST or ALT must meet criteria for resuming treatment according to the boxed warning contained within the docetaxel Prescribing Information
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1.3) should have treatment permanently discontinued

When resuming docetaxel treatment, please follow the dose reduction recommendations noted in Section 7.4.1.

8.1.3 Post Study Follow-up

In this study, EFS and pCR are multiple primary endpoints. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of

outcome and/or survival follow-up data as required and in line with [Section 2](#) 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 ([Table 2-3](#) and [Table 2-4](#)). 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 participation will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

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

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

9.1 Efficacy Assessments

The primary efficacy assessments will be EFS and pCR, and a key secondary endpoint is MPR rate (defined as number of randomized participants with $\leq 10\%$ residual tumor in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized participants for each treatment group), which will be assessed by BIPR at the time of definitive surgery. Surgery should be

performed within 6 weeks after completing up to 3 cycles (last dose) of neoadjuvant treatment. The following lymph node levels should be sampled at the time of definitive surgery:

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

Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor sample in RNA later for biomarker studies (as applicable dependent on the size of residual tumor) is mandatory on the day of surgery. Processing of the remainder of the specimens for histopathologic analysis should be performed within 72 hours of the procedure. Sections will be used for central pathology review assessing pCR and MPR. **Any tumor, tumor bed, or lymph node specimens that are reviewed locally must be submitted for central pathology review.** Gross examination on the entire specimen should be performed which includes all tumor, associated lymph node tissue, and uninvolved parenchyma. The specimen should be sectioned at 0.5 cm intervals, and blocks should be submitted for the full cross section for every other 0.5 cm interval. When estimating viable tumors, in situ carcinoma should not be included. For very large tumors with no gross evidence of response, a minimum of 1 slide/cm is required for assessment of major pathologic response. Sites are strongly encouraged to submit the diagnostic H&E stained slides assessed by the local pathologist for central pathology review. The final diagnostic pathology report must be submitted with the slides and blocks for review. Tumor sample acquisition guidelines and submission process will be outlined in the study Laboratory Manual to be provided by the central lab.

Radiographic assessments will be performed with the Schedule Activities in [Table 2-2](#).

Disease recurrence, change in tumor measurements, and tumor response will be assessed by the BICR using the RECIST 1.1 criteria.

9.1.1 Imaging Assessment for the Study

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

Screening (baseline) assessments are to be performed within 28 days prior to randomization. PET/CT with contrast should be assessed at baseline. A separate CT with contrast of the chest, abdomen, and other suspected areas (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality for RECIST 1.1 measurements. Participants with suspected brain metastases and all those with stage II disease or higher should be evaluated with MRI/CT of the brain pre- and post-contrast. Tumor assessments should be performed following RECIST 1.1 criteria.

A preoperative PET/CT with contrast should be acquired within 14 days of surgery. A separate CT with contrast of the chest, abdomen, and other suspected areas (as well as the PET/CT) is required if the CT component of a PET/CT is not sufficient diagnostic quality for RECIST 1.1 measurements.

Postoperative assessments with CT with contrast of the chest including the adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1 and then should occur every 12 weeks (± 7 days) for 2 years (104 weeks), then every 6 months (24 weeks ± 7 days) for 3 years, and then every year (52 weeks ± 7 days) for 5 years or until disease recurrence or progression confirmed by BICR. The same imaging method should be used as the screening/baseline. For participants who did not receive definitive surgery AND without tumor progression confirmed by BICR, the first tumor assessments should be done 12 weeks (± 7 days) following the tumor restaging, subsequent tumor assessments will be performed with the same frequency and methods as described for those having received definitive surgery; in case the planned initiation of subsequent anti-cancer therapy is within 12 weeks of restaging, every effort should be made to repeat tumor assessment prior to subsequent anti-cancer therapy.

Images will be submitted to the third-party radiology vendor for central review as they are performed on an ongoing basis. Sites will be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the study Imaging Manual to be provided by the radiology vendor. 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 judgement.

9.1.2 Patient-reported Outcomes

The evaluation of health-related quality of life (QoL) is an increasingly important aspect of a clinical efficacy in oncology trials. Such data provides an understanding of the impact of treatment from the participants' perspective and offers insights into the patient experience that may not be captured through physician reporting. Generic health-related QoL scales additionally provide data necessary in calculating utility values for health economic models.

Participants will be asked to complete the 3-level version of the EQ-5D before any clinical activities are performed during on-treatment clinic visits, at Post-neoadjuvant Visits 1 and 2, and at designated visits or during phone calls during the Survival Follow-up Phase. The questionnaire will be provided in the participants preferred language and may be administered by telephone during the Survival Follow-up Phase. A standardized script will be used to facilitate telephone administration of the EQ-5D-3L. [Table 2-2](#), [Table 2-3](#), and [Table 2-4](#) provide information regarding the timing of participant-reported outcomes assessments.

The EQ-5D-3L 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, 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 Japan, UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D-3L includes a visual analog scale 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 is available for use in over 150 languages.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in [Appendix 8](#).

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

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

Contacts for SAE reporting specified in Appendix 8.

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

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 the last dose of neoadjuvant therapy or 90 days after surgery, whichever is longer, and 30 days after the last dose of adjuvant therapy, at the time points 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.

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

All SAEs must be collected that occur during the screening period and 100 days after the last dose of neoadjuvant therapy or 90 days after surgery, whichever is longer, and 30 days after the last dose of adjuvant therapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.

- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in [Appendix 8](#).
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

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

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 8.

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 8)
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in [Section 9.2](#) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in [Section 8.3](#)).

Further information on follow-up procedures is given in Appendix 8.

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.

All SAEs must be collected that occur during the screening period and 100 days after the last dose of last dose of neoadjuvant therapy or 90 days after surgery, whichever is longer, and 30 days after the last dose of adjuvant therapy. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Appendix 8](#).

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

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

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

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

9.2.6 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 8](#) 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.

Definition of immune-mediated adverse events (IMAEs)

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

Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 100 days of the last dose
- regardless of causality

- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component
 - treated with immune-modulating medication (Of note, adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- Table 9.2.8-1 below provides a summary of the IMAEs category and their respective preferred terms.

Table 9.2.8-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	Preferred terms included under IMAE Category
Pneumonitis	Pneumonitis, interstitial lung disease
Diarrhea/Colitis	Diarrhea, colitis, enterocolitis
Hepatitis	Hepatotoxicity, hepatitis, hepatitis acute, autoimmune hepatitis, AST increased, ALT increased, bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, nephritis allergic, tubulointerstitial nephritis, acute renal failure, renal failure, increased creatinine
Rash	Rash, rash maculopapular

9.2.9 Management Algorithms

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered 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
- Myocardial

The above algorithms are found in the Nivolumab Investigator Brochure and [Appendix 4](#).

9.3 Overdose

All occurrences of overdose must be reported as SAEs (see [Section 9.2](#)).

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

9.4 Safety

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

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry (at rest). Screening assessments and screening laboratory assessments should be performed in accordance with [Table 2-1](#).

Pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug.

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first 2 safety (neo-adjuvant) follow-up visits, for 90 days after surgery, and for 30 days after adjuvant therapy. Once participants reach the Survival Follow-up Phase, either in-person visits or documented telephone calls/email correspondence to assess the participant's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing in accordance with [Table 2-2](#).

On treatment pregnancy tests should be performed as per the schedule in the Schedule of Activity Table.

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 Neoadjuvant and Adjuvant Follow-up Phases 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 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 treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Please refer to the Schedule of Activities in [Section 2](#) for details related to the required laboratory assessment.

9.4.2 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 ipilimumab PK assessment will be collected from participants in Arm A only. Samples for nivolumab PK assessments will be collected from participants in Arm A and Arm C described in Table 9.5-1. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples. 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 sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. PK samples will be analyzed for nivolumab and ipilimumab by a validated ligand binding assay.

Table 9.5-1: Pharmacokinetic (PK) Sample Collections for Nivolumab and Ipilimumab - Arm A and Arm C

Study Day 1 Cycle = 2 weeks for Arm A and 1 Cycle = 3 weeks for Arm C	Event (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab ^a
C1D1	0.5 (EOI) ^b	00:30	X	X

Table 9.5-1: Pharmacokinetic (PK) Sample Collections for Nivolumab and Ipilimumab - Arm A and Arm C

Study Day 1 Cycle = 2 weeks for Arm A and 1 Cycle = 3 weeks for Arm C	Event (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab ^a
C2D1	Predose ^c	00:00	X	X
C3D1	Predose ^c	00:00	X	X

^a PK blood samples for ipilimumab were be collected from Arm A participants only.

^b EOI: End of Infusion. This sample should be taken immediately (ie, within 5 minutes) prior to stopping ipilimumab infusion in Arm A or nivolumab infusion in Arm C. 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.

^c Predose sample should be collected just before the administration of nivolumab (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.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

9.8.1 Additional Research Collection

Additional research retention are mandatory for all study participants, except where prohibited by local laws or regulations, ethics committees, institutional requirements, or where a waiver is provided by BMS or their designee. Where one or more of these exceptions occurs, participation in the additional research should be encouraged, but will not be a condition of overall study participation. Study participants may opt out of the additional research.

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

This retention for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb Company 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 participants. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

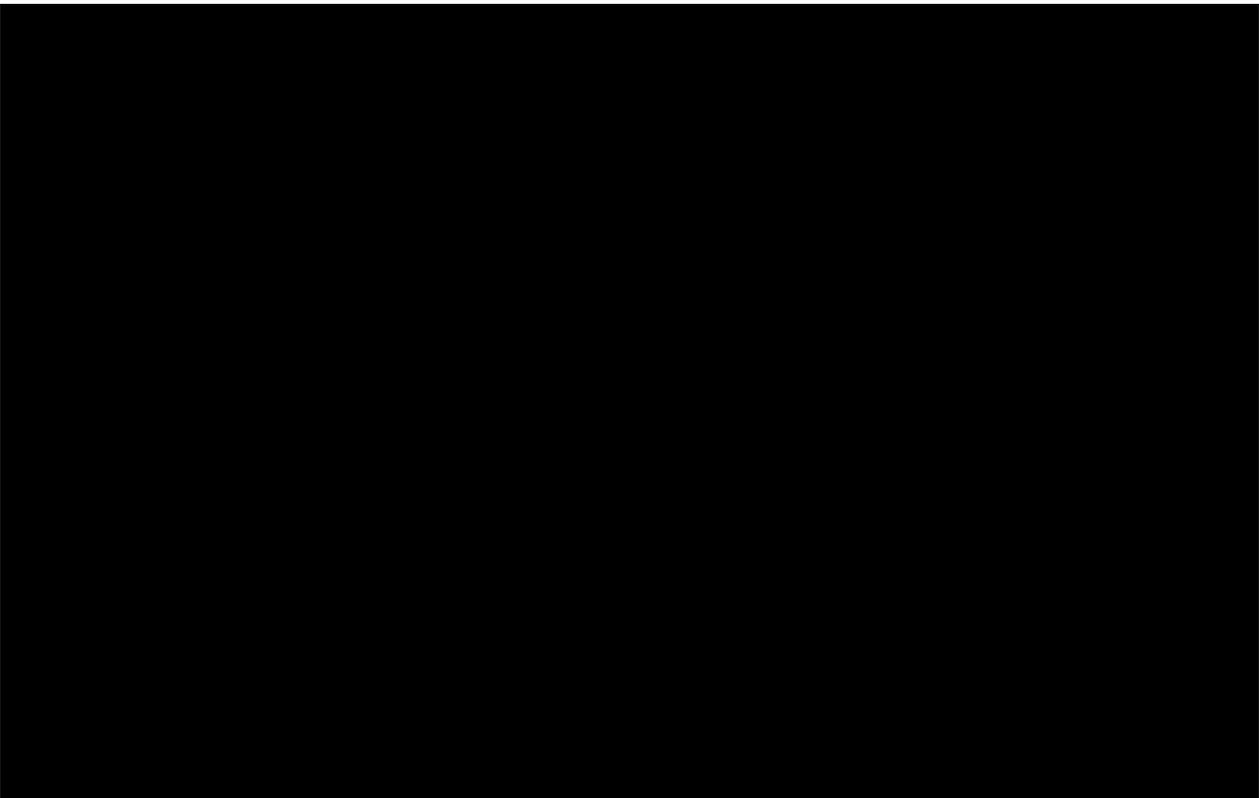
All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.



Samples kept for future research will be stored at the BMS Biorepository [REDACTED] 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; no researcher will have access to the key, which is securely held by the Investigator at the clinical site, so that there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

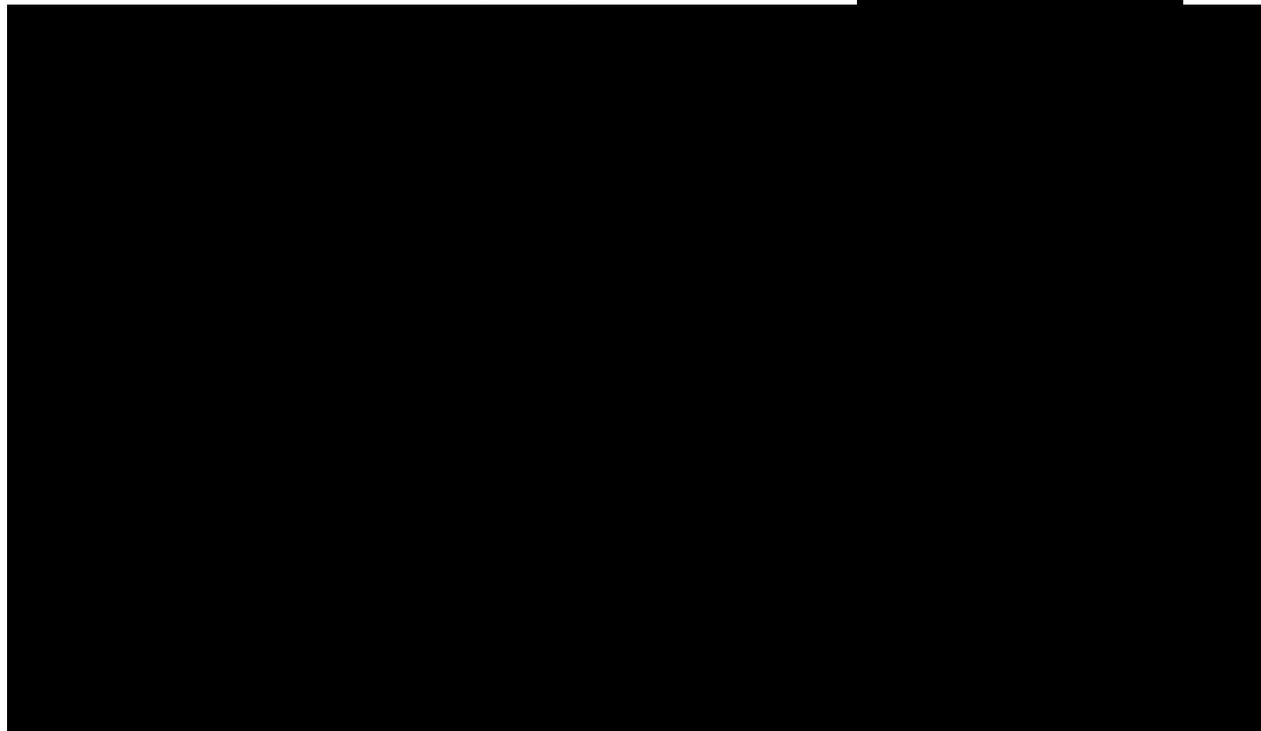


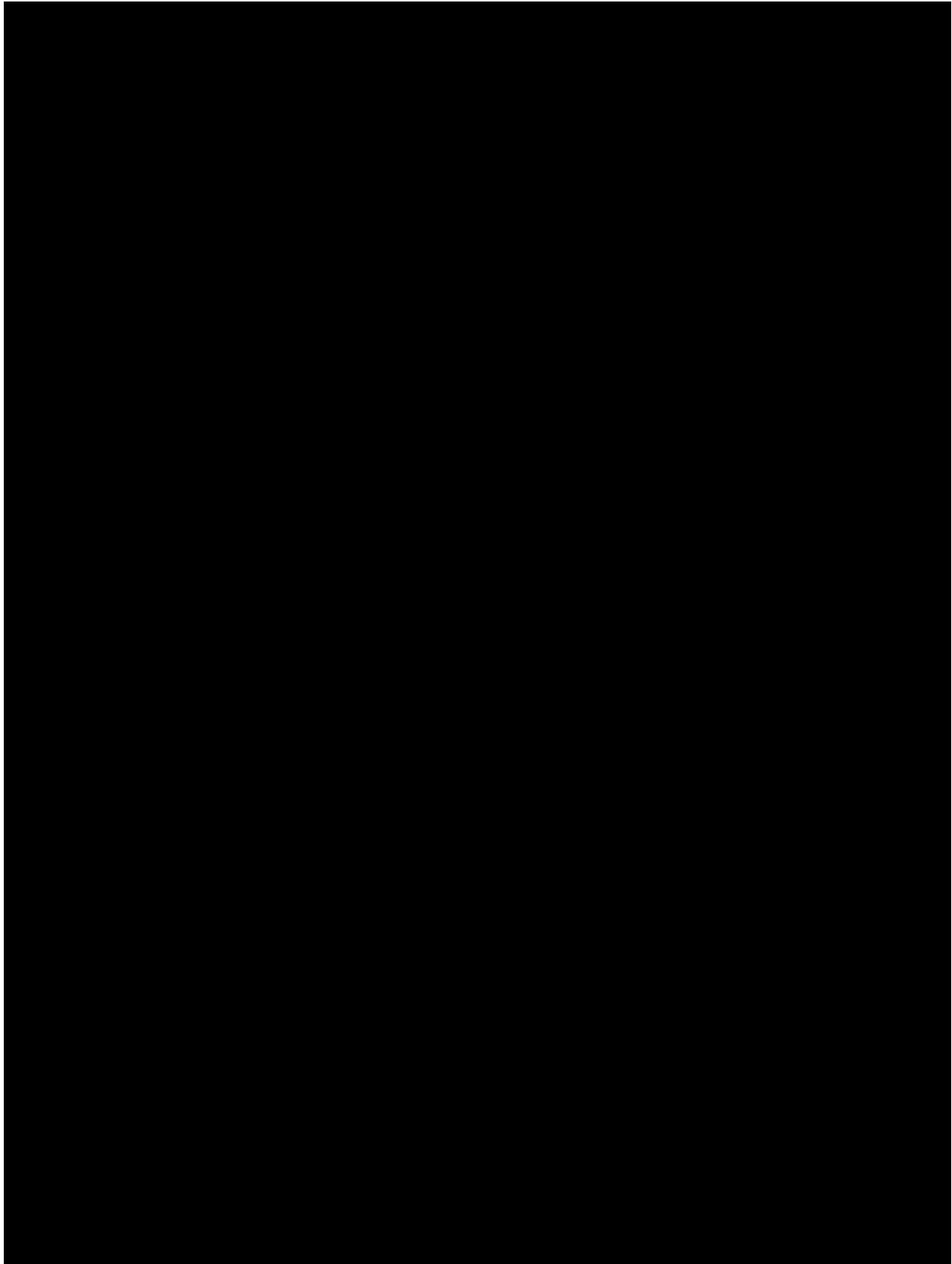


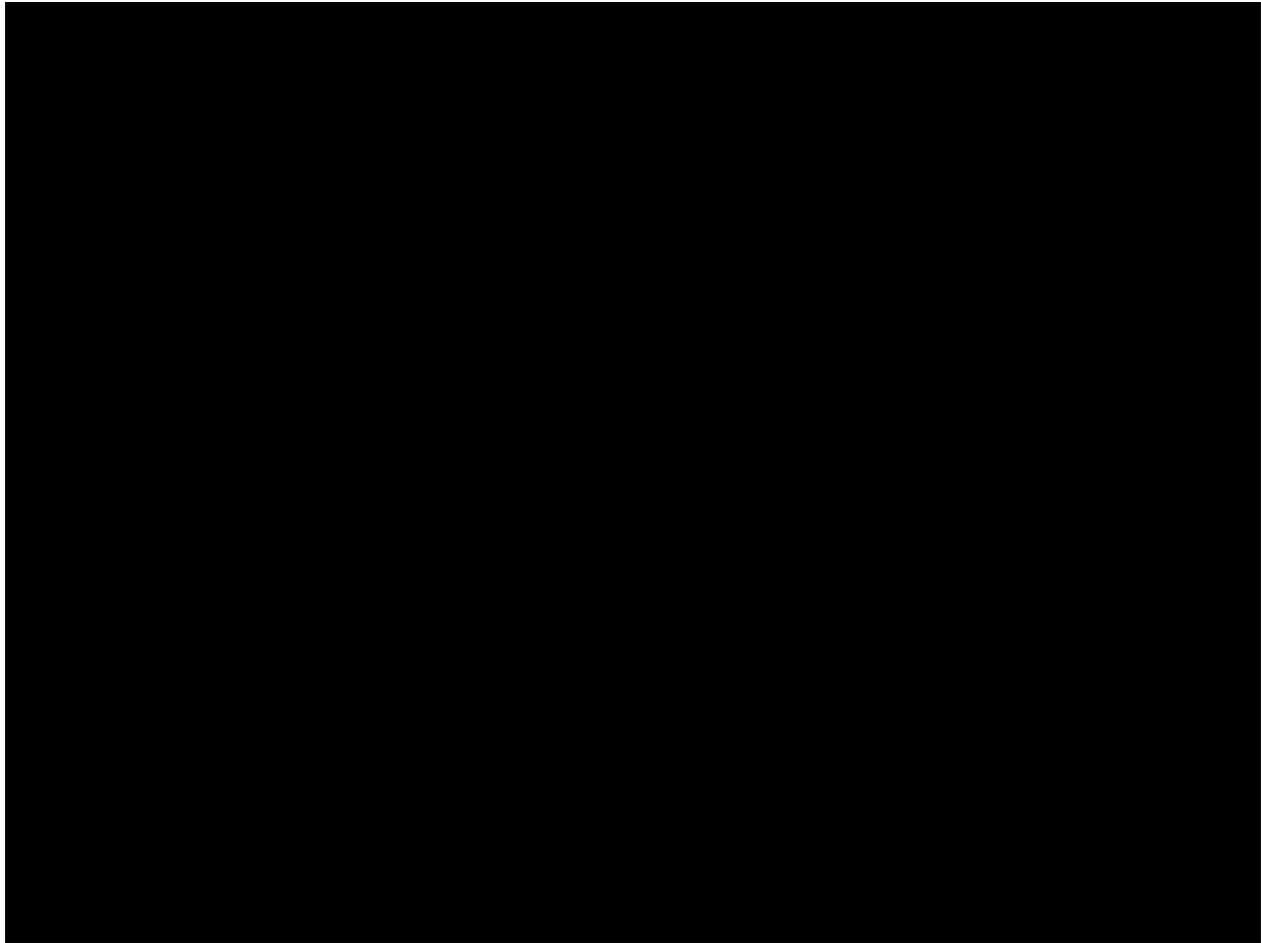
9.8.1.1 Tumor Tissue Specimens

Archival (slides [blocks/slides] \leq 3 months) FFPE tumor tissue collected at initial diagnosis is required for study entry. Samples will be sent to a third party to stain and score for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx kit (Dako). Stained tissue samples will be assessed by a pathologist at a central lab identified by the Sponsor and scored as PD-L1 expressing if membrane staining is observed in \geq 1% tumor cells among a minimum of 100 evaluable tumor cells. If an archived specimen is not available, a fresh tumor biopsy will be collected. Additional tumor will be collected during surgical resection, which will be after 3 cycles of treatment in each arm. A third (optional) biopsy will be collected at the time of disease progression. The third biopsy will not be collected in China.

Collected tumors may be further analyzed by additional modalities







9.8.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Exploratory	<p>Proportion of delayed or canceled surgery, duration of surgery, length of hospital stay, surgical approach, incidence of AE/SAE associated with surgery, including pneumonitis, ARDS, re-admission to the Intensive Care Unity, atrial fibrillation or other supraventricular tachycardia up to 90 days after surgery will be summarized by treatment group using descriptive statistics.</p> <p>The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.</p> <p>The safety analysis will be performed in all treated participants. The rate of treatment-related selected AEs and SAEs in each treatment arm will be summarized. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All treatment-emergent 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, thyroid function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.</p>



9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.10 Other Assessments

9.10.1 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
- Pulmonary function capacity (eg, FVC, FEV1, TLC, FRC, and DLco) 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 IB (≥ 4 cm), II or resectable IIIA (N2) 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) prior to randomization. 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 by segmentectomy or wedge resection will not be accepted. If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling and evaluation will have occurred, though complete mediastinal lymph node dissection (MLND) is preferred. 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 or MLND locations are required:

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

If there is clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node areas, the participant will be considered eligible if no lymph nodes are found in those areas.

Participants should have a PET/CT scan with contrast of the base of the skull through the upper thigh performed within the 14 days prior to planned surgery to assess for clinical response. A separate CT with contrast of the chest, abdomen, and other suspected areas (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality of RECIST 1.1 measurements. Surgery should be performed within 6 weeks of completing up to 3 cycles (last dose) of neoadjuvant treatment.

9.10.2 Post-surgical Evaluation:

The first tumor assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1. Afterwards, radiographic assessment will be performed every 12 weeks (± 7 days) for 2 years) following surgery, every 6 months (± 7 days) for 3 years, and then every year (± 7 days) for 5 years or until recurrence or progression of disease is documented.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The original study design (before Revised protocol 01) had two arms, with participants randomized in a 1:1 ratio to either neoadjuvant nivolumab plus ipilimumab or platinum doublet chemotherapy arm. Revised protocol 02 added a new, neoadjuvant nivolumab plus platinum doublet chemotherapy arm. When the third arm opens and as each site receives IRB/EC approval of revised protocol 02, the IRT will switch to a 1:1:1 randomization at the respective site. Starting from that point on, the site will only enroll under revised protocol 02.

Revised protocol 03 withholds randomization into the arm of neoadjuvant nivolumab plus ipilimumab but continues randomizing eligible participants into either neoadjuvant nivolumab plus platinum doublet chemotherapy arm or platinum doublet chemotherapy arm in a 1:1 ratio. Approximately 350 participants (175 participants per arm) will be randomized between 2 arms neoadjuvant nivolumab plus platinum doublet chemotherapy or platinum doublet chemotherapy from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03. Participants already randomized in the original 2-arm part (neoadjuvant nivolumab plus ipilimumab vs neoadjuvant chemotherapy) and in the arm of neoadjuvant nivolumab plus ipilimumab in 3-arm part defined by revised protocol 02 will remain in trial and continue scheduled trial procedures. It is expected to have around 70 participants randomized in the original 2-arm part and approximately another 75 participants randomized in the arm of neoadjuvant nivolumab plus ipilimumab in the 3-arm part. It is estimated that there will be a total of approximately 500 participants on the study.

Starting from 1:1:1 randomization, approximately 350 participants will be randomized to the 2 arms neoadjuvant nivolumab plus platinum doublet chemotherapy or platinum doublet chemotherapy in a 1:1 ratio. The sample size of the study is calculated based on the primary endpoint of EFS and accounts for the multiple primary endpoints comparisons: pCR (per BIPR) and EFS (per BICR) with an initial alpha allocation of 0.01 and 0.04 respectively. Formal analyses of pCR and EFS may be conducted at different timepoints. The fallback method will be used, ie, if the pCR comparison between Arm C and Arm B is statistically significant, then 0.01 alpha allocated to pCR will be passed to the EFS comparison for Arm C vs Arm B and the EFS

comparison will be conducted at the $\alpha = 0.05$ level. If the pCR comparison between Arm C and Arm B is not statistically significant, then the EFS comparison for Arm C vs Arm B will be conducted at the $\alpha = 0.04$ level. In addition, if EFS is significant, OS will be tested hierarchically at the same level as EFS.

10.1.1 Pathologic Complete Response (pCR)

The primary analysis of pCR will be performed after 350 randomized participants in neoadjuvant nivolumab plus platinum doublet chemotherapy and platinum doublet chemotherapy (from start of 1:1:1 randomization) have an opportunity for surgery.

Assuming an accrual rate of 10 participants (all comers) a month between Arms B and C during 1:1:1 randomization (about 10 months), and 15 participants per month during 1:1 randomization, it is anticipated that the 350 participants will be randomized in approximately 27 months. The pCR endpoint is expected to be analyzed after about 30 months from start of 1:1:1 randomization.

The sample size of 350 participants is based on the EFS endpoint. With this sample size, assuming pCR rate of 10% on Arm B chemotherapy and 30% on Arm C nivolumab plus chemotherapy, respectively, the 350 participants will provide more than 90% power to detect an odds ratio of 3.857 with a 2-sided type I error of 1%.

It is estimated that there will be about 110 subjects randomized to Arm A neoadjuvant nivolumab plus ipilimumab before revised protocol 03 is implemented. Assuming true pCR rate is 15% on this arm, there is 95% probability that the lower bound of 95% exact confidence interval of pCR is above 5%.

10.1.2 Event Free Survival (EFS)

For the formal comparison of EFS as assessed by BICR for nivolumab plus platinum doublet chemotherapy (Arm C) vs platinum doublet chemotherapy (Arm B), only participants randomized from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03 will be counted.

The power details are provided below using $\alpha = 0.05$ (0.01 α from the pCR endpoint fallback to the EFS comparison), considering this protocol amendment (protamend07) occurs after the statistically significant pCR final analysis but before any analysis of EFS or OS. In addition, the accrual reflects 358 participants who were actually concurrently randomized in Arms B and C.

A total of 185 events ensure that an overall 2-sided 5% significance level sequential test procedure with 2 interim analyses occurring after 148 events (80% of events required for final analysis) and 167 events (90% of events required for final analysis) in 358 randomized participants will have 82% power assuming an HR of 0.65 between the 2 arms. Considering a piecewise exponential distribution with control hazard rates of 0.028 before 20 months, 0.017 between 20 months and 40 months, 0.014 between 40 and 60 months, and 0.008 after 60 months, and a dropout rate of approximately 20%, it is anticipated the EFS analyses will take place at approximately 48, 58, and 73 months from the start of 1:1:1 randomization. The trigger of the first interim analysis is event driven. The second interim analysis will take place when 167 events are observed [REDACTED]. The final analysis will take place [REDACTED].

when approximately 185 events are observed [REDACTED]. The stopping boundaries at the interim and final EFS analyses will be derived based on the exact number of events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analyses of EFS are performed at exactly 148 and 167 events, the nominal significance level for EFS superiority will be 0.024 and 0.030, respectively. The nominal significance level for the final look of EFS after 185 events would then be 0.038.

Table 10.1.3-1 summarizes the key parameters of the sample size justification in the randomized participants.

10.1.3 Power Consideration for Overall Survival (OS)

The secondary endpoint OS will be tested hierarchically after EFS with the same overall alpha as for the EFS comparison (two-sided 4% if the pCR comparison is not significant or 5% if the pCR comparison is significant).

For the formal comparison of OS for nivolumab plus platinum doublet chemotherapy (Arm C) vs platinum doublet chemotherapy (Arm B), only participants concurrently randomized from 1:1:1 randomization in revised protocol 02 and 1:1 randomization in revised protocol 03 will be included. Three interim analyses for OS are planned to occur at the time of EFS interim and final analyses, only if EFS is significant.

The power details are provided below using $\alpha = 0.05$ (0.01 alpha from the pCR endpoint fallback to the EFS comparison, then hierarchically on the OS comparison), considering this protocol amendment (protamend07) occurs after the readout of the statistically significant pCR final analysis but before any analysis of EFS or OS. In addition, they reflect the 358 participants that were actually concurrently randomized in Arms B and C:



Table 10.1.3-1: Power Calculation for EFS and OS

	EFS Arm C vs Arm B	OS Arm C vs Arm B
Accrual	Actual accrual 25 months	Actual accrual 25 months
Power	82%	
Two-sided alpha	0.05	0.05
Hypothesized median control vs exp (months)	28 vs 52*	
Hypothesized hazard ratio	0.65	
Sample size for concurrent comparison	358	358
First interim analysis for EFS (EFS IA1) and OS (OS IA1)	148 events Alpha boundary: 0.024	Triggered by EFS IA1 [Redacted]
Second interim analysis for EFS (EFS IA2) and OS (OS IA2)	167 events [Redacted] Alpha boundary: 0.030	<ul style="list-style-type: none"> If EFS IA1 not significant: triggered by EFS IA2.
Final EFS (EFS FA) and third OS (OS IA3) interim analysis	185 events [Redacted] Alpha boundary: 0.038	<ul style="list-style-type: none"> If EFS IA2 not significant: triggered by EFS FA.
Final OS analysis (OS FA)	-	

*Calculated from piecewise exponential distribution

EFS, event free survival; FA, final analysis; IA, interim analysis; OS, overall survival

10.1.4 Analyses Timing Projections

The pCR analysis occurred with a database lock on 16-Sep-2020.

Considering the actual enrollment, it will take:

- Approximately 48 months when 148 events on Arms B and C (after start of 1:1:1 randomization) are observed for the first interim analysis (EFS IA1, OS IA1). This is about 54 months from first patient first visit (FPFV) of the study. This analysis will be triggered by the number of EFS events.
- Approximately 58 months when 167 EFS events on Arms B and C (after start of 1:1:1 randomization) are observed for the second interim analysis (EFS IA2, OS IA2). This is approximately 64 months from FPFV. [REDACTED]
- Approximately 73 months when 185 EFS events on Arms B and C (after start of 1:1:1 randomization) are observed for the final EFS analysis (EFS FA, OS IA3). This is about 79 months from FPFV of the study. [REDACTED]

10.2 Populations for Analyses

Population	Description
All enrolled participants	All participants who signed an informed consent form and were registered into the IRT
All randomized participants	All participants who were randomized to any treatment arm in the study. This is the primary dataset for analyses of study conduct, study population and efficacy.
All concurrently randomized participants in Arms B and C	All randomized participants on Arms B and C after 1:1:1 randomization. Analysis of demography, protocol deviations, baseline characteristics, and primary efficacy analyses will be performed for this population.
All treated participants	All participants who received any dose of study medication in neoadjuvant setting. This is the primary dataset for drug exposure and safety analysis.
PK participants	All participants with available serum time-concentration data from randomized participants dosed in Arm A and Arm C

10.3 Statistical Analyses

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	<p>The fallback method will be used for the hypothesis testing of the two primary endpoints pCR and EFS. Initially, the type 1 error of 0.05 will be allocated as follows: 0.01 will be allocated to the pCR comparison between Arm C and Arm B, and 0.04 will be allocated to the EFS comparison between Arm C and Arm B. If the pCR comparison between Arm C and Arm B is statistically significant, then 0.01 alpha will be passed to the EFS comparison for Arm C vs Arm B and the test comparison will be conducted at the alpha = 0.05 level.</p> <p>pCR analysis will be based on all concurrently randomized participants in Arms B and C analysis population. pCR rate will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. For pCR rate comparison between arms C vs B, the difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a 2-sided, 1% alpha level. The odds ratios stratified by PD-L1, disease stage (IB/II vs IIIA) and gender (Mantel-Haenszel estimator) between Arms C and B will be provided along with the 99% CI. In addition, an estimate of the difference in pCR rates and corresponding 99% CI will be calculated using CMH methodology and adjusted by stratification factors (PD-L1, disease stage (IB/II vs IIIA) and gender).</p> <p>pCR rate will also be computed for subjects randomized to Arm A neoadjuvant nivolumab plus ipilimumab along with the exact 95% CI using Clopper-Pearson method.</p> <p>EFS is defined as time from randomization to any of the following events: any documented progression of disease precluding surgery, progression or recurrence disease (based on BICR assessment per RECIST 1.1) after surgery, or death due to any cause. Participants who don't undergo surgery for reason other than progression will be considered to have an event at RECIST 1.1 progression (based on BICR) 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 did 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 censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.</p> <p>If the pCR analysis comparing Arms C vs B is statistically significant, a two-sided alpha of 0.05 will be used for the comparison of EFS in Arms C vs B. If the pCR analysis comparing Arms C vs B is not statistically significant, a two-sided alpha of 0.04 will be used for the comparison of EFS in Arms C vs B. EFS among the all concurrently randomized participants in Arms B and C analysis population will be tested. The distribution of EFS will be compared between Arm C vs Arm B via a 2-sided, log rank test stratified by the randomization stratification factor (ie, PD-L1, disease stage [IB/II vs IIIA] and gender). The hazard ratio and the corresponding (1-adjusted alpha) confidence interval will be estimated for Arm C vs Arm B in a stratified Cox proportional hazards model using the randomized arm as a single covariate. The EFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method using a log-log transformation. In addition, EFS rates at 1, 2, 3, and 4 years 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).</p> <p>Sensitivity analysis on EFS will also be performed, and details will be included in statistical analysis plan.</p>
Secondary	<p>At the time of pCR analysis, MPR rate will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in MPR rates between Arm C and Arm B and corresponding 95% CI will be calculated using CMH methodology and adjusted by stratification factors (PD-L1, disease stage (IB/II vs IIIA) and gender).</p>

Endpoint	Statistical Analysis Methods
	<p>OS curves, OS medians with 95% CIs, and OS rates at 1, 2, 3, and 4 years with 95% CIs will be estimated using Kaplan-Meier methodology. HR and corresponding 2-sided 95% CI will be estimated for Arm C vs Arm B using a Cox proportional hazards model with treatment group as a single covariate, stratified by randomization stratification factors. If tested, the distribution of OS will be compared between Arm C vs Arm B in the all concurrently randomized participants in Arms B and C population via a 2-sided, log rank test stratified by the randomization stratification factors.</p> <p>Time to death or distant metastases (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 using BICR according to RECIST 1.1. Participants who die without a reported distant metastasis will be considered to have experienced an event on the date of their death. Patients 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. Participants who did not have baseline scan, or participants who did not have any on-study tumor assessments and did not die, will be censored on the date they were randomized.</p> <p>TTDM curves, TTDM medians with 95% CIs, and TTDM rates at 1, 2, 3, and 4 years with 95% CIs will be estimated using Kaplan-Meier methodology. HR and corresponding 2-sided 95% CI will be estimated for Arm C vs Arm B using a Cox proportional hazards model with treatment group as a single covariate, stratified by randomization stratification factors. There will be no formal comparison of TTDM.</p>
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.2 Other Analyses

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

The EQ-5D-3L questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point. Summary statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum) for the EQ-5D-3L utility index and VAS scores, as well as their corresponding changes from baseline, will be tabulated by treatment and planned time point. In the base case, index scores will be derived using the UK weighting algorithm. In addition, the proportion of participants reporting no, moderate, or severe problems in each of the 5 EQ-5D-3L dimensions will be summarized by treatment group at each time point. Proportions will be based on the number of participants assessed at assessment time point. A by-participant listing of the level of problems in each dimension, corresponding EQ-5D-3L health state (ie, 5-digit vector), EQ-5D-3L index score, and EQ-5D VAS score will be provided.

10.3.3 Interim Analyses

There is no interim analysis for the pCR endpoint.

Two formal interim analyses for EFS are planned after approximately 148 and 167 events have been observed on Arms B and C, after the start of 1:1:1 randomization, which is projected to occur approximately 48 and 58 months after start of 1:1:1 randomization. [REDACTED]

[REDACTED] The formal comparisons of EFS will allow for early stopping for superiority. An independent statistician external to BMS will perform the analysis. If the study continues beyond the second interim analysis, the final analysis will be conducted after 185 EFS events have been observed on Arms B and C from the start of 1:1:1 randomization. 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.

[REDACTED]

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12 APPENDICES



APPENDIX 1 TNM STAGING SYSTEM FOR LUNG CANCER (7TH EDITION)

Table -1: International Association for the Study of Lung Cancer Definitions for T, N, and M Descriptors			
T (Primary Tumor)			
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without invasion more proximal than the lobar bronchus		
T1a	Tumor ≤ 2 cm in diameter		
T1b	Tumor > 2 cm but ≤ 3 cm in diameter		
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features Involves main bronchus, ≥ 2 cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T2a	Tumor > 3 cm but ≤ 5 cm		
T2b	Tumor > 5 cm but ≤ 7 cm		
T3	Tumor > 7 cm or any of the following: Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; main bronchus < 2 cm distal to the carina (without involvement of the carina) Atelectasis or obstructive pneumonitis of the entire lung Separate tumor nodule in same lobe		
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or without separate tumor nodules in a different ipsilateral lobe		
N (Regional Lymph Nodes)			
N0	No regional lymph node metastasis		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
M (Distant Metastasis)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage Groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0

Table -1: International Association for the Study of Lung Cancer Definitions for T, N, and M Descriptors			
Stage IIA	T1a, T1b, T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a, T1b, T2a, T2b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N3	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

Adapted from Goldstraw P, Crowley J, Chansky K, et al. 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 Oncol. 2007 Aug;2(8):706-14.



APPENDIX 2 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 Company
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl ⁻	chloride
cm	centimeter
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form, paper or electronic
cRR	clinical response rate
dL	deciliter
DMC	Data Monitoring Committee
EBUS	endobronchial ultrasound
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	event-free survival

Term	Definition
eg	exempli gratia (for example)
FA	final analysis
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IA	Interim analysis
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ie	id est (that is)
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
LC	liquid chromatography
LDH	lactate dehydrogenase

Term	Definition
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MPR	major pathological response
MLND	mediastinal lymph node dissection
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
NSCLC	non-small cell lung carcinoma
NIMP	non-investigational medicinal products
OS	overall survival
PBMC	peripheral blood mononuclear cells
pCR	Pathologic complete response
PFS	progression-free survival
PK	pharmacokinetics
PPK	Population pharmacokinetic
PO	per os (by mouth route of administration)
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
SNP	single nucleotide polymorphisms
SOC	Standard of care
SOP	Standard Operating Procedures

Term	Definition
t	temperature
WHO	World Health Organization
WOCBP	women of childbearing potential



APPENDIX 3 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, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.



APPENDIX 4 NIVOLUMAB 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.

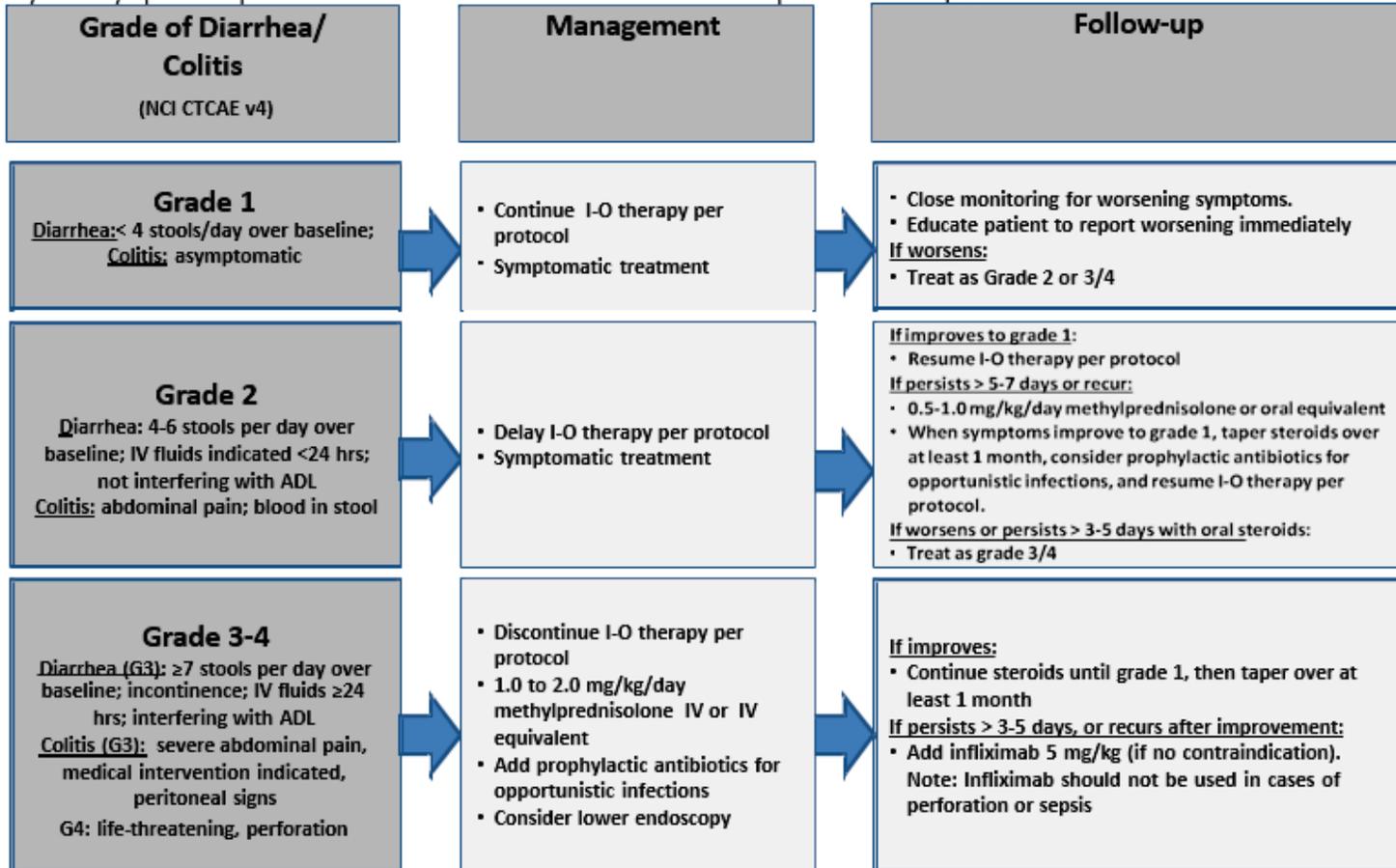
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

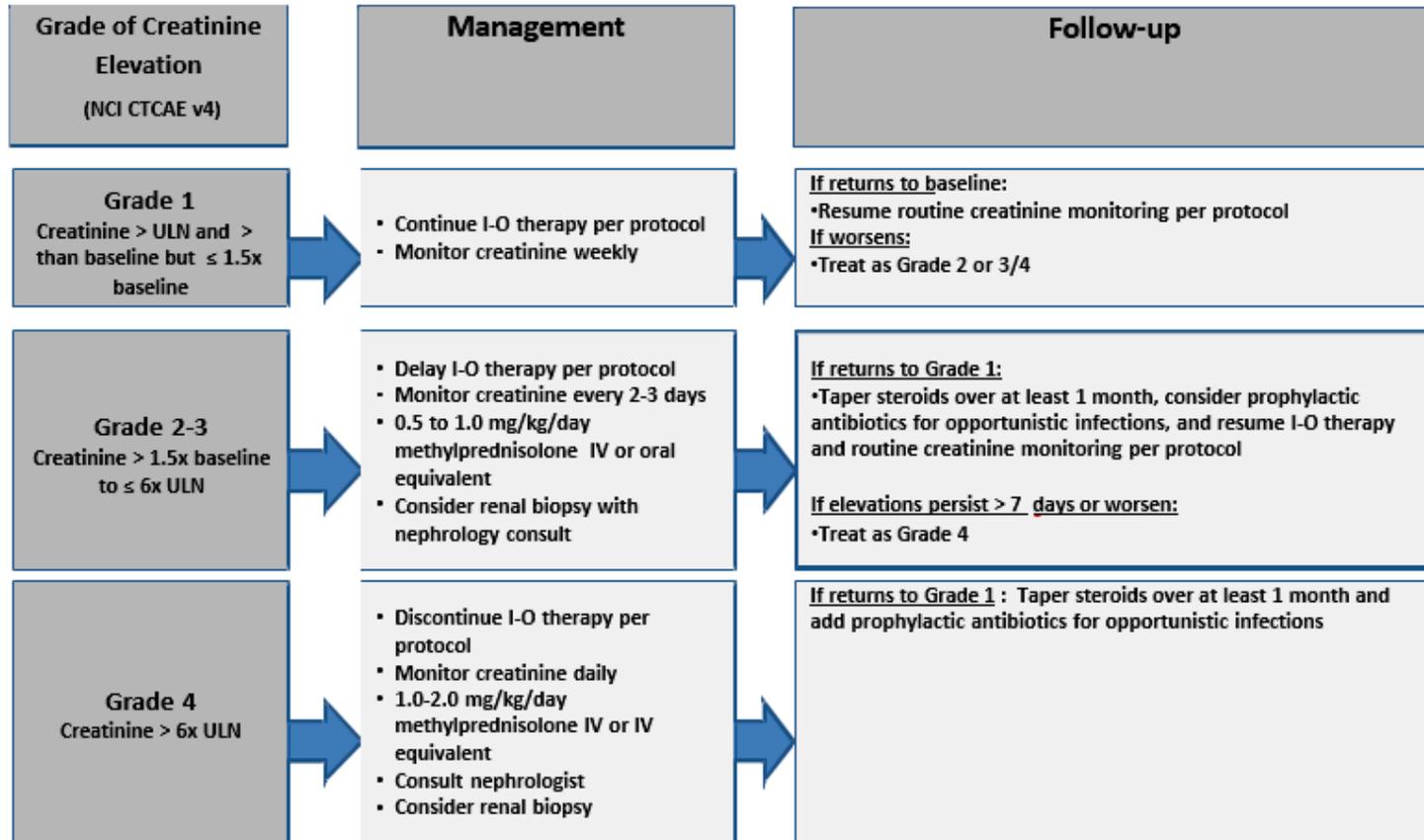


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

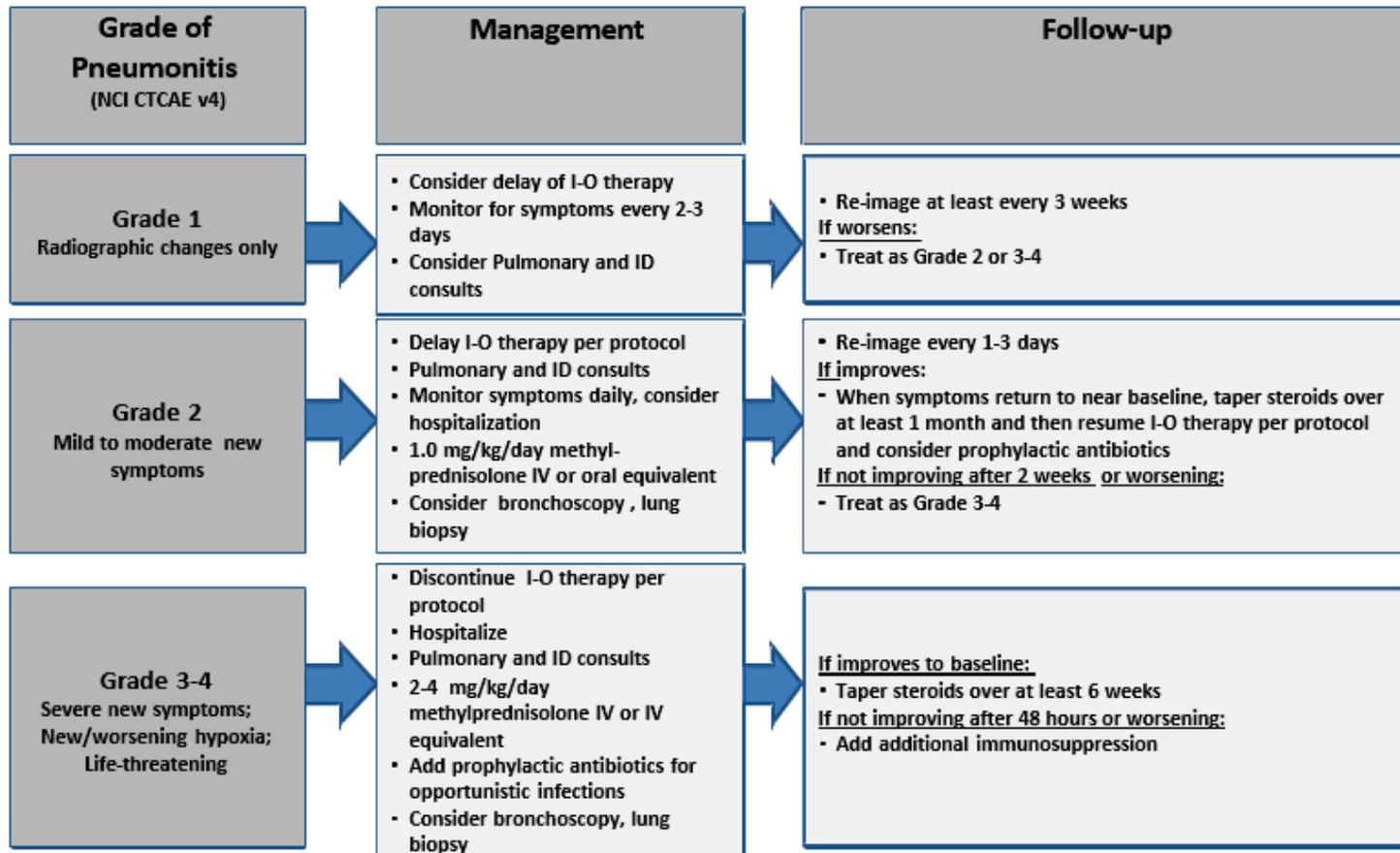


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

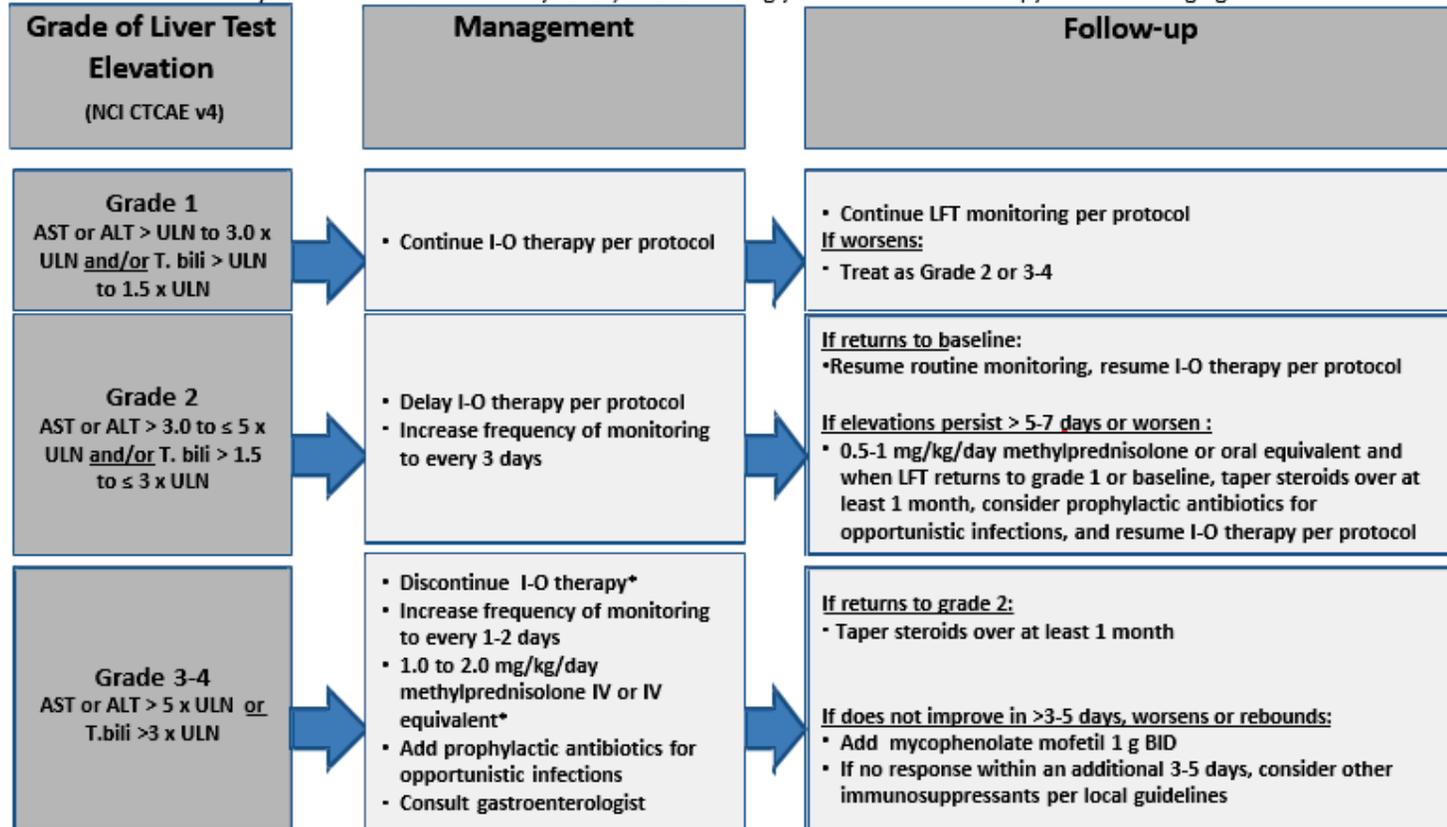


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



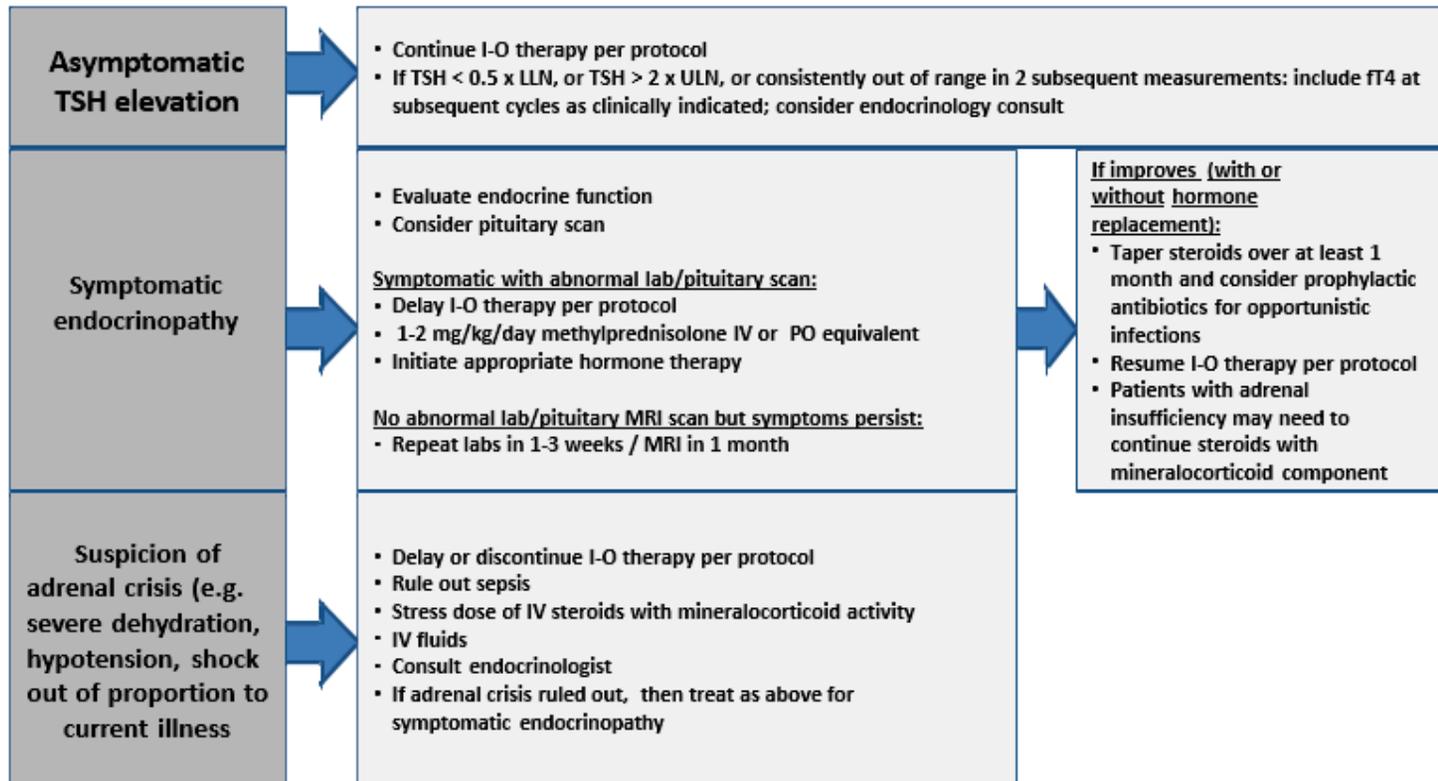
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

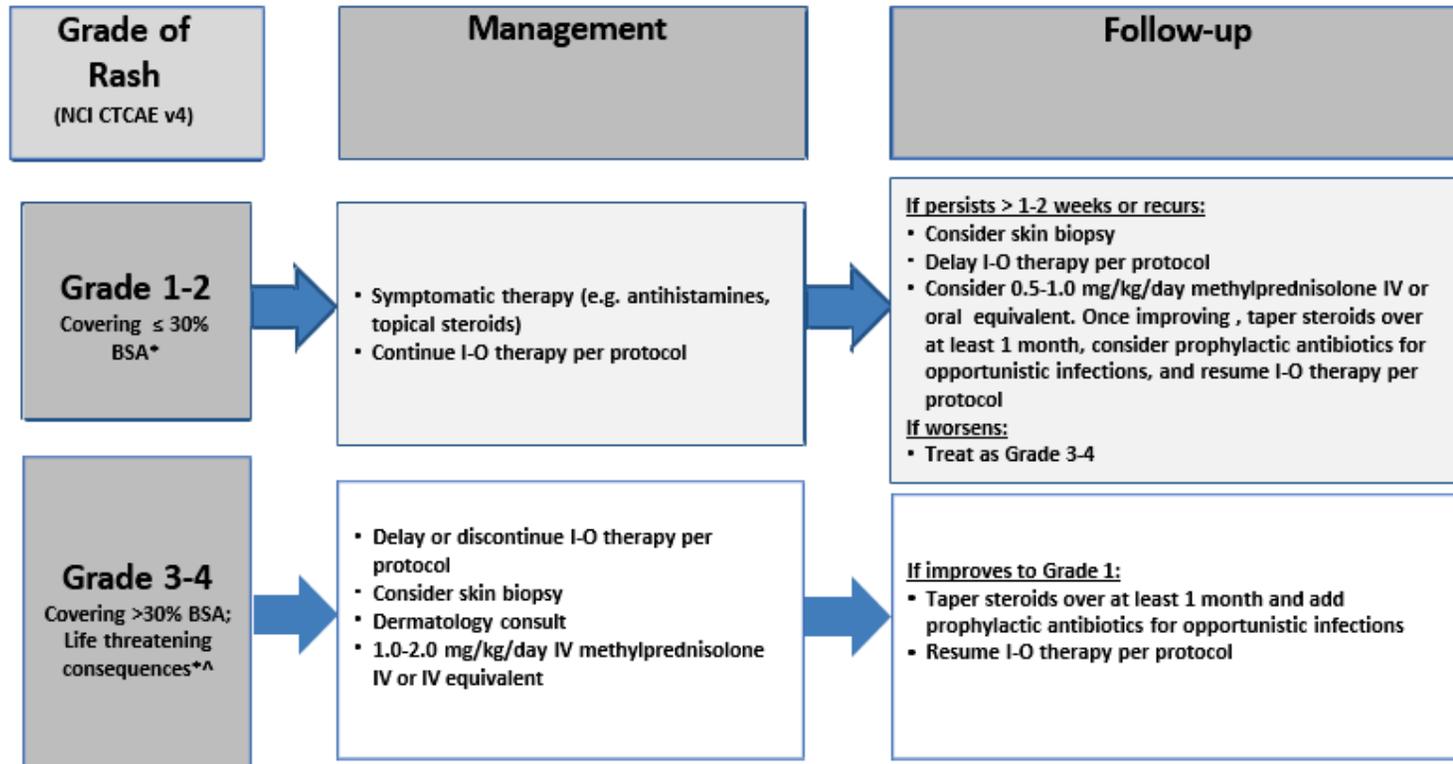


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

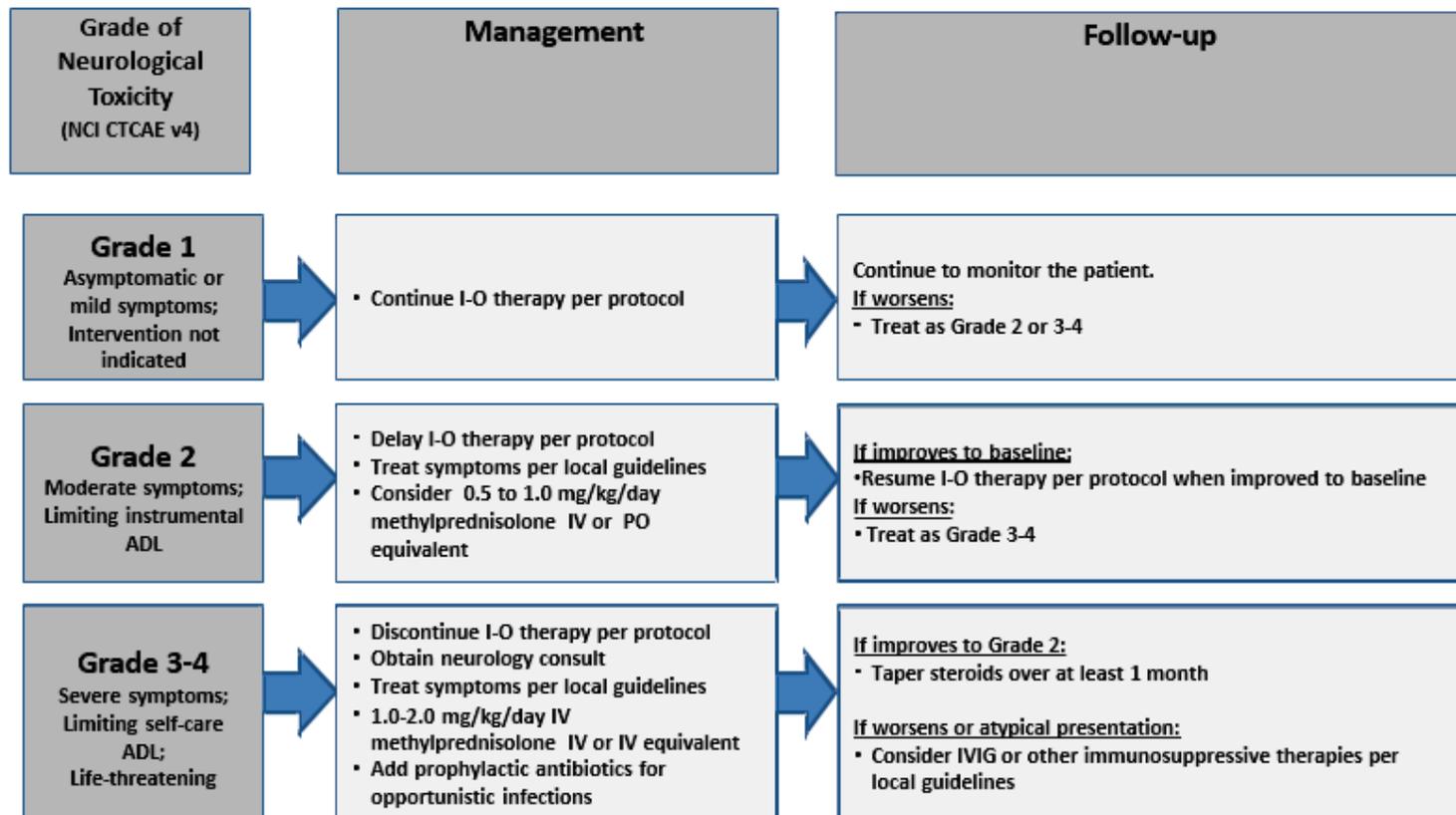
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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

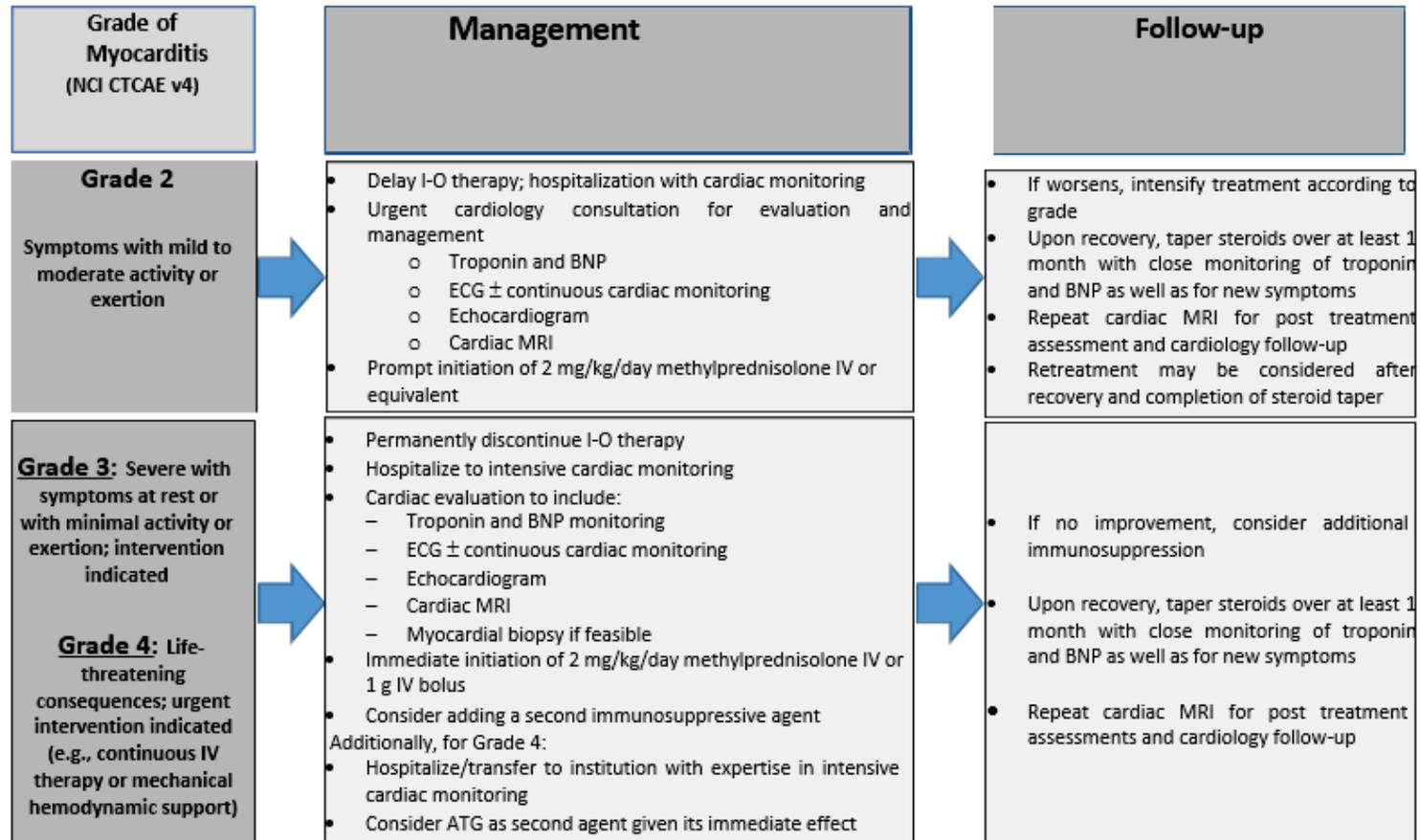
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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 5 RESPONSE CRITERIA (RECIST 1.1)

1 EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized 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:

- 1) 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 2) 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 3) 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT 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 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.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, 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.

2 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).

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 nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 RESPONSE CRITERIA

3.1 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.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 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.

3.1.1.2 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 (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.

3.1.1.3 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’.

3.2 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 and normalization of tumor marker level. 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) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

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

3.2.1.1 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 (see further details below). A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. 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.

3.2.1.2 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 a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols 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.

3.2.2 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.

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.

If a new lesion is equivocal, for example because of its small size, continued therapy and 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:

- 4) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 5) 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.

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

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

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. [Table 3.3.2-1](#) 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 3.3.2-2](#) is to be used.

Table 3.3.2-1: Time Point Response - Patients With Target (+/- Non-Target) Disease			
Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 3.3.2-2: 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.

3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in [Table 3.3.3-1](#).

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

Table 3.3.3-1: Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR ^a
CR	SD	SD provided minimum criteria for SD duration ^b met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration ^b met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration ^b met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration ^b met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration ^b met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

^b Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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.

APPENDIX 6 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

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

Highly Effective Contraceptive Methods That Are User Dependent

<i>Failure rate of <1% per year when used consistently and correctly.^a</i>
--

- | |
|---|
| <ul style="list-style-type: none">• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b<ul style="list-style-type: none">– oral– intravaginal– transdermal• Progestogen-only hormonal contraception associated with inhibition of ovulation^b |
|---|

<ul style="list-style-type: none">- oral- injectable
Highly Effective Methods That Are User Independent
<ul style="list-style-type: none">• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^b• Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)^c• Intrauterine device (IUD)^c• Bilateral tubal occlusion
<ul style="list-style-type: none">• Vasectomized partner <p><i>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.</i></p>
<ul style="list-style-type: none">• Sexual abstinence <p><i>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.</i></p> <ul style="list-style-type: none">• It is not necessary to use any other method of contraception when complete abstinence is elected.• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: ^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. ^b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. ^c Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness



Unacceptable Methods of Contraception
<ul style="list-style-type: none">• 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• Periodic abstinence (calendar, symptothermal, post-ovulation methods)• Withdrawal(coitus interruptus).• Spermicide only• Lactation amenorrhea method (LAM)

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 the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- 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 treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of 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 7 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:

- Good 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 GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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 (e.g., 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 (e.g., 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 (e.g., 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 for
- 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 to 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 (i.e., 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 unable to give their written consent (e.g., stroke or subjects 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
<p>Supplied by BMS (or its vendors):</p>	<p>Records or logs must comply with applicable regulations and guidelines and should include:</p> <ul style="list-style-type: none"> • 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.
<p>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)</p>	<p>The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include:</p>

If	Then
	<ul style="list-style-type: none"> • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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.

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 (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., 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 (e.g., 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, i.e., 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 this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

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

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) 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 CTA.

APPENDIX 8 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
<ul style="list-style-type: none">• 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
<ul style="list-style-type: none">• 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

<p>Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:</p>
<p>Results in death</p>
<p>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)</p>
<p>Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)</p> <p>NOTE:</p> <p>The following hospitalizations are not considered SAEs in BMS clinical studies:</p> <ul style="list-style-type: none"> • 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)
<p>Results in persistent or significant disability/incapacity</p>
<p>Is a congenital anomaly/birth defect</p>
<p>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.)</p>

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 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

OVERALL RATIONALE FOR REVISED PROTOCOL 06, 14-Jul-2020

During recent interactions with health authorities (2020), they indicated that the early event-free survival (EFS) interim analysis (IA) may lack robustness due to immature data. Accordingly, the EFS IA plan was changed in protocol revision 06 to remove the first planned IA.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number and Name	Description of Change	Brief Rationale
Synopsis, Objectives and Endpoints Table 4-1 Objectives and Endpoints Table 10.3.1 Efficacy Analyses	Clarified that any progression precluding surgery is an EFS event and that RECIST 1.1 progression/recurrence per blinded independent central review (BICR) applies post surgery or for participants without surgery	Clarified EFS definition
Synopsis, Number of Participants 5.2 Number of Participants	Corrected the number of participants	To align with 10.1 Sample Size Determination
5.3 End of Study Definition 10.1.2 Event Free Survival 10.1.3 Power Consideration for Overall Survival (OS) Table 10.1.3-1 Power Calculation for EFS and OS 10.1.4 Analyses Timing Projections Table 10.1.4-1 Scheduled Analyses, Criteria, and Projected Timelines 10.3.3 Interim Analyses	Removed the first of 2 IA of EFS and updated alpha spending on the remaining single interim and final analyses of EFS	Health authorities suggested that the early EFS IA may lack robustness at that level of data maturity
10.1.2 Event Free Survival 10.1.4 Analyses Timing Projections Table 10.1.4-1 Scheduled Analyses, Criteria, and Projected Timelines	Clarified that actual timing of analyses may differ from projected timing	Clarified potential variation in analyses timing
10.1.2 Event Free Survival	Removed text about descriptive EFS analysis	Descriptive analyses for the DMC will be described in the DMC Charter
All	Corrected typographical errors	Minor, so not specified



OVERALL RATIONALE FOR REVISED PROTOCOL 05, 18-Sep-2019

The revised protocol updates analyses projections for pCR and EFS and clarifications of surgery exploratory endpoints, instruction for biomarker collection and pathology review, and rules for PD-L1 stratification. Additionally, management algorithms were updated for myocarditis.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 05		
Section Number and Name	Description of Change	Brief Rationale
Synopsis Section 4 Objectives and Endpoints	Updated exploratory endpoint to include completeness of resection in surgical approach	Update provides clarity on collection of surgical outcomes
Synopsis Section 5.1 Overall Design	Updated stratification of participants with PD-L1 not evaluable/ indeterminate status to PD-L1 negative participants	Update provides clarity for stratification of participants with PD-L1 not evaluable/ indeterminate status
Synopsis	Language updated to identify the CA209816 Laboratory Manual as a source for pathology specimen collection and processing. Additionally, blinded pathology review process will assess for confirmation of endpoints.	Updates provide instruction for guidelines for collection and processing of pathology specimens and confirmation of endpoints
Section 5.3 End of Study Definitions	Updated the timing of pCR rate	Provides updated projection of analysis for pCR rate.
[REDACTED]		
Section 9.8.1.1 Tumor Tissue Specimens	Clarified tumor biopsy collection will not be collected in China	Sites are unable to collect optional tumor biopsy in China.
Section 10.1 Sample Size Determination Section 10.1.1 Pathologic Complete Response (pCR) Sections 10.1.4 Analyses Timing Projections Section 10.2 Populations for Analyses Section 10.3.1 Efficacy Analyses Section 10.3.3 Interim Analyses	Updates anticipated sample size and projected timing of analyses for pCR and EFS	Provides updated information for analysis for pCR and EFS..
Section 10.3.1 Efficacy Analyses	Updated statistical analysis methods for TTDM	Statistical analysis methods for TTDM were updated.
Appendix 4 Management Algorithms	Updated management algorithms to include myocarditis	Aligns management algorithms with updated Investigator Brochure

OVERALL RATIONALE FOR REVISED PROTOCOL 04, 25-Jun-2019

The CA209816 revised protocol 04 adds EFS on next line of therapy as an exploratory objective. Statistical analyses, power calculations, projected timelines [REDACTED]. Additional changes were added for clarity.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number and Name	Description of Change	Brief Rationale
Synopsis Table 4-1: Objectives and Endpoints	Added exploratory endpoint of Event Free Survival on next line of therapy	Added EFS on next line of therapy, as provides additional follow-up information for efficacy and survival
Section 7.7.1 Prohibited and/or Restricted Treatments	Added the concomitant administration of substances that are also tubularly secreted (eg, probenecid) could potentially result in delayed clearance of pemetrexed.	Added to comply with HA request
Section 10.2.1 Populations for Analysis at Pathologic Complete Response Analysis Timepoint	Clarified the pCR analysis population	Updated section for clarity
Synopsis Section 5.1 Overall Design Section 5.1.1 Data Monitoring Committee and Other External Committees	<ul style="list-style-type: none"> BICR confirmation of progression should not be requested if investigator judges the progression will not preclude surgery. Tumor assessments (if clinically feasible) and BICR should continue even after the initiation of subsequent anti-cancer therapies. 	Updated parameters for BICR confirmation for clarity
Section 10.1.3 Power Consideration for Overall Survival (OS) Table 10.1.3-1: Power Calculation for EFS and OS Section 10.3.3 Interim Analyses	Added power consideration for OS testing	In case of significant EFS, OS will be tested.
Section 10.1.4 Analyses Timing Projections Table 10.1.3-1 Scheduled Analyses, Criteria, and Projected Timelines	Updated the analysis timing projections	Updated the analysis timing projections
Appendix 8 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting Adverse Events	Updated AE template language	Updated appendix to align with program standards

OVERALL RATIONALE FOR REVISED PROTOCOL 03, 21-Sep-2018

The CA209816 revised protocol closes enrollment in Arm A (nivolumab plus ipilimumab) and expands the sample size in Arm B (chemotherapy) and Arm C (nivolumab plus chemotherapy). Subsequently, the study rationale and statistical section was updated to support the new analyses. Additional changes were made to provide clarity in study conduct.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number and Name	Description of Change	Brief Rationale
Synopsis, Objectives, Overall Design, Schema, Number of Participants Section 4 Objectives and Endpoints Section 5.1 Overall Design Section 5.2 Number of Participants	Enrollment in Arm A (nivolumab plus ipilimumab) was stopped and randomization of participants (1:1 ratio) into Arm B and C will continue enrolling for a total of 350 participants	Study design was changed to support nivolumab plus chemotherapy as neoadjuvant therapy in NSCLC based on emerging data.
Synopsis, Objectives Section 4 Objectives and Endpoints	<ul style="list-style-type: none"> Updated objectives for assessments of Arm B to Arm C Added time to death or distant metastases (TTDM) as secondary objective Updated tertiary objectives for Arm A (nivolumab and ipilimumab) 	Objectives were updated to align with change in study design
Synopsis Overall Design	Participants with large-cell neuroendocrine carcinoma tumor histology are excluded	Eligibility criteria was updated as protocol's chemotherapy regimens are not optimal for treating this specific subtype of NSCLC
Synopsis Treatment Arms and Duration, Study Treatment Section 5.1 Overall Design Section 5.4.6 Rationale for Choices of Platinum-based Chemotherapy Doublet Table 7-1 Study Treatments for CA209816 Section 7.1 Treatments Administered Table 7.1-1 Selection and Timing of Doses Section 7.4 Dose Modifications	Additional platinum doublet chemotherapy regimen (paclitaxel/carboplatin) was added	Additional platinum doublet chemotherapy regimens (paclitaxel/carboplatin) added to reflect knowledge gained from emerging data.
Section 7.4.1.1 Platinum Doublet Chemotherapy - Dose Reductions for Hematologic Toxicity Section 7.4.1.2 Platinum Doublet Chemotherapy - Dose Reductions for Non-Hematologic Toxicities	Updated and moved dose modification for docetaxel into hematologic toxicity and non-hematologic toxicity sections.	Updated dose modification for docetaxel into correct sections of protocol.
Section 7.4.2.2 Dose Delay Criteria for Platinum Doublet Chemotherapy	Provided updated dose delay criteria for chemotherapy	Provided updated dose delay criteria for safety

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number and Name	Description of Change	Brief Rationale
Table 2-3 Post Neoadjuvant Period for Those Participants Not Receiving Adjuvant Therapy Section 9.1.1 Imaging Assessment for the Study	<ul style="list-style-type: none"> Updated time relationship between adjuvant radiotherapy and tumor imaging assessments Clarified imaging for tumor assessments for participants who do not proceed to definitive surgery 	Updated imaging assessment requirements for clarity
Section 5.3 End of Study Definition Section 10.1 Sample Size Determination Section 10.1.1 Pathologic Complete Response (pCR) Section 10.1.2 Event Free Survival (EFS) Section 10.1.3 Analyses Timing Projections Section 10.3.1 Efficacy Analyses Section 10.3.3 Interim Analyses	Statistical analysis plan was updated	Statistical analyses were updated to align with change in study design.
Section 3.2.1 Indication Background Section 3.2.4 Nivolumab Combined with Ipilimumab Clinical Activity Section 3.2.5 Immuno-oncology Treatment Combined with Chemotherapy Clinical Activity Section 3.3 Benefit/Risk Assessment Section 5.4.3 Rationale for Immuno-oncology Treatment in Neoadjuvant NSCLC Section 5.4.3.1 Rationale for Combination of Nivolumab and Ipilimumab (Arm A) Section 5.4.3.2 Rationale for PD-1 Inhibitor with Chemotherapy (Arm C) Section 5.4.4 Rationale for Pathologic Response	Rationale, background information, and trial schematic were updated	Rationale, background information, and trial schematic were updated to align with changes in study design and current data.
Table 2-1 Screening Procedural Outline Table 2-2 Neoadjuvant Period Procedural Outline	Updated to include FVC, FEV1, TLC, FRC, and DLco.	Parameters of pulmonary function tests to be collected were clarified.
Section 9.5 Pharmacokinetics	Time window of Cycle 1 Day 1 end-of-infusion PK sampling for Arm A and C was clarified	Time window for certain PK sample collection was provided.
Appendix 4 Hepatic Adverse Event Management Algorithm	Footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT $\leq 8 \times$ ULN or T.bili $\leq 5 \times$ ULN was removed.	Language was modified to align protocol with current Nivolumab Investigator Brochure and nivolumab program safety management principals.

OVERALL RATIONALE FOR REVISED PROTOCOL 02, 06-JUL-2017

The CA209816 study has been revised in response to a health authority request to add the primary objective of event-free survival for the study population. In addition, a new treatment arm was added to the study as a new comparison for the current treatment landscape.

This revised protocol applies to all current and future participants.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number and Name	Description of Change	Brief Rationale
Title; Section 1 Synopsis, Objective and Endpoints, Study Design, Number of Participants, Treatment Arms and Duration; Section 2 Schedule of Activities; Section 3.1 Study Rationale, Research Hypothesis; Section 4 Objectives and Endpoints; Section 5 Study Design; Section 5.2 Number of Participants; Section 5.3 End of Study Definition; Section 6 Study Population; Section 7 Treatment; Section 9.5 Pharmacokinetics; Section 10 Statistical Considerations (Sections 10.1.1, 10.1.2, 10.1.3, 10.2, 10.3, 10.3.3)	A new treatment arm of nivolumab plus platinum doublet chemotherapy (Arm C) was added to the study. The sample size was increased to 642 with the addition of the new treatment arm.	New treatment arm was added for current treatment landscape.
Title, Section 1 Synopsis, Objective and Endpoints, Study Design, Number of Participants, Treatment Arms and Duration; Section 2 Schedule of Activities' Section 3.1 Study Rationale; Section 3.2; Section 4 Objectives and Endpoints; Section 5 Study Design (Section 5.1, Schema, Section 5.2, Number of participants, Section 5.3 End of Study Definition; Section 9.1 Efficacy Assessments; Section 10 Statistical Considerations (Sections 10.1.1, 10.1.2, 10.1.3, 10.2 Populations for Analyses, 10.3 Statistical Analyses, 10.3.3)	Primary objectives were modified to event free survival and pathological response.	New multiple primary objective was added in response to health authority request.
Synopsis, Background Section 3.2 (Sections 3.2.4, 3.2.5); Section 3.3 Benefit/Risk Assessment, Background, Section 5.4 Scientific Rationale for Study Design (Sections 5.4.3, 5.4.4, 5.5.2)	With the addition of new treatment arm and new primary endpoints, the background and rationale were updated with current safety and efficacy data.	Study sections were updated to reflect current study design and available data on safety and efficacy of study treatments.