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Clinical Protocol CA209078

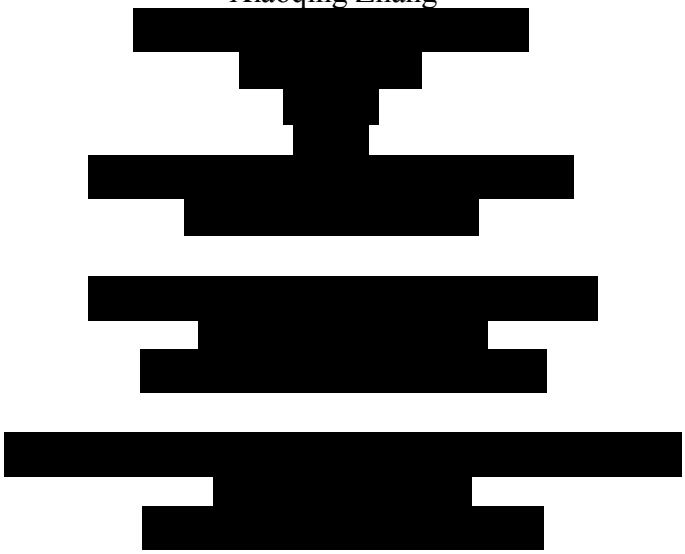
An Open-label Randomized Multinational Phase 3 Trial of Nivolumab versus Docetaxel in Previously Treated Subjects with Advanced or Metastatic Non-small Cell Lung Cancer

(CheckMate 078: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 078)

Revised Protocol Number: 05
Incorporates amendment(s) 05

Study Director/Medical Monitor

Xiaoqing Zhang



Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

Clinical Protocol CA209078

(CheckMate 078: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 078)

Protocol Title: An Open-label Randomized Multinational Phase 3 Trial of Nivolumab versus Docetaxel in Previously Treated Subjects with Advanced or Metastatic Non-small Cell Lung Cancer

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): For subjects randomized to nivolumab, they will be dosed intravenously over 60 minutes at 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or other reasons specified in the protocol. For subjects randomized to docetaxel, they will be dosed intravenously over 60 minutes at 75 mg/m² every 3 weeks until disease progression, unacceptable toxicity, or other reasons specified in the protocol.

Amendment 05 Update:

Optional Switch of Arm B Subjects Receiving Docetaxel Treatment to Nivolumab 3mg/kg Q2 Weeks (Arm A) Under Amendment 05, subjects treated with docetaxel will have the option to switch to intravenous nivolumab 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or other reasons specified in the protocol.

Study Phase: 3

Research Hypothesis: The treatment effect of nivolumab is consistent between the study population and subjects from global pivotal trials (CheckMate 057 and CheckMate 017) and nivolumab increases OS as compared with docetaxel, in subjects with advanced or metastatic NSCLC who have failed prior platinum-based doublet chemotherapy.

Objectives:

Primary:

- To demonstrate that the OS benefit of nivolumab in this study population with advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy is consistent with benefit observed in global studies CheckMate 057 and CheckMate 017.
- To compare the OS of nivolumab versus docetaxel in subjects with advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.

Secondary: Secondary objectives include the following:

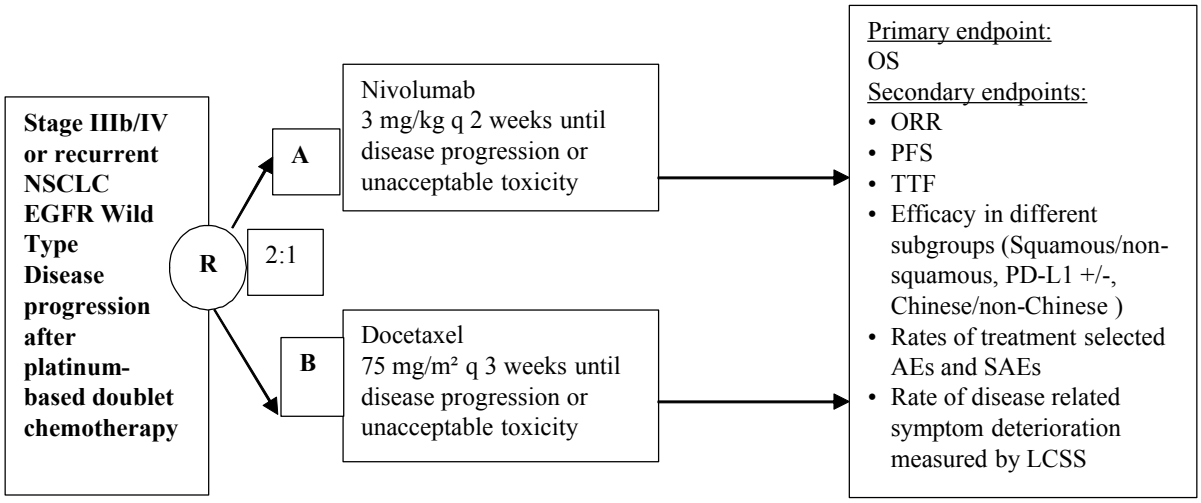
- To compare the objective response rate (ORR) of nivolumab versus docetaxel.
- To compare the progression-free survival (PFS) of nivolumab versus docetaxel.
- To compare the time to treatment failure (TTF) of nivolumab versus docetaxel
- To evaluate clinical efficacy (OS, ORR, and PFS) in different subgroups, including squamous and non-squamous NSCLC subgroups, PD-L1 positive and PD-L1 negative protein expression subgroups, and Chinese and non-Chinese subgroups.
- To evaluate the rate of treatment related selected AEs and SAEs in nivolumab and docetaxel arms.
- To evaluate the proportion of subjects exhibiting disease-related symptom deterioration by Week 12 and by Week 24, as measured by the Lung Cancer Symptom Scale (LCSS), in nivolumab and docetaxel arms.

[redacted]

Study Design: This is an open-label, randomized, Phase 3 study in adult (≥ 18 years old) male and female subjects with advanced or metastatic NSCLC after failure of prior platinum-doublet chemotherapy. Approximately 500 subjects, will be randomized to nivolumab vs docetaxel in a 2:1 ratio.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned in a 2:1 ratio to one of two treatment arms (see Study Design and Duration schema in Figure 1 below). Randomization will be stratified and balanced according to the following factors: histology (squamous vs non-squamous)/ PD-L1 Status (positive vs negative/unevaluable)/ ECOG Performance status (0 vs 1). Approximately 100 PD-L1 unevaluable subjects will be randomized

Figure 1: Study Design



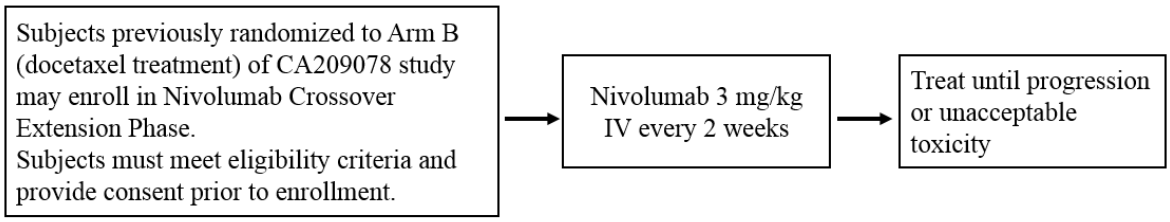
Amendment 05 Update: Subjects currently receiving treatment with nivolumab (Arm A) will continue to be treated and monitored as specified in the protocol.

With this amendment, all subjects randomized to Arm B docetaxel treatment who meet eligibility criteria may enter the Nivolumab Crossover Extension Phase, according to the schema below. These subjects will follow the assessment schedules outlined in Table 5.1-7 of the protocol.

Subjects treated with docetaxel who have ended study treatment will be able to receive treatment with nivolumab via the crossover extension phase of the study, assuming basic inclusion/exclusion criteria are met (including a 3-week washout period for prior systemic anti-cancer therapy). Details are provided in Sections 3.3.1 and 3.3.2.

Subjects currently receiving treatment with docetaxel should continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from docetaxel in the judgment of the investigator. These subjects may receive nivolumab once they are discontinued from docetaxel therapy, assuming basic inclusion/exclusion criteria are met (including a 3-week washout period from last dose of docetaxel).

Figure -2: Nivolumab Crossover Extension Phase Schema for Subjects Previously Randomized to Docetaxel



Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.5.4. Treatment beyond progression for subjects in the nivolumab crossover extension

phase must be approved by the BMS Medical Monitor prior to subjects receiving additional study drug. Criteria for discontinuation of treatment beyond progression are described in Section 4.5.4. Subjects who discontinue study therapy for reasons other than progression should continue to be scanned until disease progression is documented.

Study Population: Subjects must meet all eligibility criteria specified in Sections 3.3.1 and 3.3.2 of the protocol, including the following:

Key Inclusion Criteria (See Protocol Section 3.3.1 for full list of criteria)

1. Subjects with histologically- or cytologically-documented NSCLC who present with Stage IIIB/IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrence of progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease)
2. Subjects must have experienced disease progression during or after one prior platinum-containing doublet chemotherapy (carboplatin or cisplatin) regimen for advanced or metastatic disease.
   - Subjects who received maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and progressed are eligible.
   - Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.
   - Subjects with recurrent disease > 6 months after platinum containing adjuvant, neoadjuvant or definite chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum- doublet regimen given to treat the recurrence, are eligible.
3. Subjects must have measurable disease disease by CT or MRI per RECIST 1.1 criteria (per Appendix 2). Radiographic Tumor Assessment performed within 28 days prior to randomization.
   a) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.
4. Males and Females ≥ 18 years of age.
5. ECOG performance status of ≤ 1.
6. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 10 unstained slides (submission of less than 10 unstained slides may be acceptable after approval by BMS Medical Monitor) of tumor sample (archival or recent) must be available for biomarker evaluation at a central laboratory. In order to be randomized; subjects will be classified as PD-L1 positive, PD-L1 negative or PD-L1 unevaluable. Biopsy should be excisional, incisional or core needle. Fine needle biopsies, drainage of pleural effusions with cytospins or punch biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable
7. Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to randomization. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to randomization

Key Exclusion Criteria (See Protocol Section 3.3.2 for full list of criteria)

1. Subjects with carcinomatous meningitis.
2. Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
3. Subjects with an active, known or suspected autoimmune disease are excluded. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorder (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

4. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
5. Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.
6. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
7. Prior treatment with docetaxel.
8. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus antibody (HCV Ab) indicating acute or chronic infection.
9. Active Tuberculosis (TB) infection based on chest X-ray, sputum tests, and clinical examination. Patients with a history of active TB infection within last 1 year are excluded even if it was treated; Patients with a history of active TB infection greater than 1 year ago are eligible if there is no evidence of active TB in current status in the investigator's opinion
10. Subjects with EGFR mutation regardless of mutation type are excluded. Non squamous subjects with unknown EGFR mutation status must be tested for EGFR mutation (use of PCR based test is strongly encouraged). If the EGFR mutation is positive, subject is excluded.
11. Subjects with known ALK translocation are excluded

Amendment 05 Update: Specific eligibility criteria for subjects originally randomized to the Arm B docetaxel treatment and now entering the Nivolumab Crossover Extension Phase are included in Section 3.3.1.1 and Section 3.3.2.1.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209078		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	10 mg/ml	IP
Docetaxel	40 mg/ml	IP
Docetaxel	20 mg/ml	IP
Dexamethasone	4 mg	Non IP

Study Assessments: This is an open-label, multinational, randomized, Phase 3 study in adult (≥ 18 years old) male and female subjects with advanced or metastatic NSCLC after failure of prior platinum-doublet chemotherapy. Subjects will be randomized to nivolumab vs docetaxel in a 2:1 ratio.

Overall survival (OS) is the primary endpoint of this study. The final analysis will be performed when a total of 382 OS events have occurred. There will be one interim analysis of OS (DMC monitored) when at least 291 OS events have been observed (76% of total events). A Time To treatment Failure (TTF) interim analysis (DMC monitored) will be conducted after the first approximately 380 randomized patients have been followed for at least 8 months.

Amendment 05 Update: The schedule of study assessments for subjects randomized to the Arm B docetaxel treatment and now entering the Nivolumab Crossover Extension Phase are included in the protocol in Section 5.1.

Statistical Considerations:

Sample Size: The sample size is calculated in order to compare the overall survival (OS) between subjects randomized to receive nivolumab and subjects randomized to receive docetaxel. Approximately 500 subjects will be randomized to the nivolumab and docetaxel arms in a 2:1 ratio. At least 382 deaths will be required for the final analysis of OS. A formal OS interim analysis will be conducted when at least 291 OS events (76% information fraction) have been observed. In absence of cross over (no use of anti-PD-1/PD-L1 agents as subsequent therapy in the docetaxel arm), average hazard ratios, calculated from the simulations, are 0.70 and 0.67 at interim and final analysis of OS, respectively. To compare OS between nivolumab and docetaxel, the weighted log-rank test will be used. The weighted log-rank test will provide 98% power (cumulative) at final analysis and 86% at interim OS, using a 2-sided overall type 1 error of 5%. The impact of crossover on power is described in Section 8.1. Significance levels at interim and final analysis of OS are calculated using the Lan-DeMets error spending function. Accrual information used in the simulations had the same pattern as the actual data at time of the protocol amendment (500 subjects were accrued in 11 months). Heterogeneity of treatment effects among histology and PD-L1 status subgroups was considered for the calculation of overall power and number of events at interim and final analyses of OS. Exponential distributions of OS times are assumed in the Docetaxel arm, with median OS of 10 months for the Squamous (SQ) and 12 months for the Non Squamous (NSQ) population. For the SQ subjects from nivolumab arm, a hazard ratio of 0.6 (mOS nivolumab vs docetaxel: 16.7 vs 10 months) and exponential distribution of OS times are assumed. For NSQ subjects from nivolumab arm, piecewise exponential models are used to model survival function. For the NSQ PD-L1 positive subjects, a 4-month delay effect (exponential distribution with mOS of 12 months) followed by an exponential distribution with mOS of 24 months was used in the model, providing an overall mOS of 20 months. For the NSQ PD-L1 negative subjects, the piecewise exponential model considered for the first 2 months an exponential distribution with mOS of 5 months; and beyond Month 2, an exponential distribution with mOS of OS 18 months, providing an overall mOS of 12.8 months.

In absence of cross-over, interim and final analyses of OS are projected to occur approximately at 24 months (13 months of minimum follow-up) and 37 months (26 months of minimum follow-up) respectively.

At both IA OS and FA OS, a consistency check will be performed first followed by a superiority test (hierarchical testing). Consistency was defined if the observed HR for OS maintains at least 50% of the risk reduction of death in the global studies after adjusting for the patient distribution and the use of anti-PD-1/PD-L1 agents in the docetaxel arm. Probability of Technical Success (PTS) of the consistency check is 95% and 98% at IA and FA OS, in absence of cross over.

Time to Treatment failure (TTF) interim analysis is expected to occur approximately16 months after study initiation. TTF will be compared across treatment groups using a weighted log rank test, population for TTF analysis is the first ~380 randomized subjects with minimum 8 months follow-up. With one-sided type 1 error of 0.025, the power for the weighted log rank test of TTF is ~95% per simulations using data observed in global pivotal studies (CheckMate 057 and 017), adjusted for the proportion of squamous and non-squamous population in this study. Estimated median HR for TTF is 0.7.

Endpoints:

Primary Endpoint and Analyses:

The primary endpoint for the study is OS. It is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while patients are on the study drug and every 3 months via in-person or phone contact after subjects go off the study drug.

At both the interim OS analysis and final OS analysis, a 2-step hierarchical testing will be performed. First, a check for consistency with global data in HR for OS will be performed. This is to mitigate loss of power due to confounding effects of cross-over (subjects receiving anti PD-1/PD-L1 agents in the comparator arm). Consistency in OS benefit is defined as maintaining 50% of the risk reduction of death from CheckMate 057 and CheckMate 017 after adjusting for the patient distribution and the use of anti-PD-1/PD-L1 agents in the docetaxel arm.

If consistency in OS with global data is demonstrated, superiority for OS will be tested. The distribution of OS in two randomized arms will be compared at the interim and final analyses via a two-sided α (adjusted for the interim), weighted log-rank test stratified by the stratification factors used for randomization as determined per IVRS, ie, histology (squamous vs non-squamous)/ PD-L1 Status (positive vs negative/non evaluable)/ ECOG Performance status (0 vs 1). The weighted log-rank test will use G (rho = 0, gamma = 1) weights, in the terminology of Fleming

and Harrington. The hazard ratio (HR) and the corresponding 100x (1- alpha)% confidence interval (CI) (adjusted for the interim) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate with the same stratification factors mentioned above. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method. Survival rates at 6, 12, and 18 months will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood formula.

This study design includes one interim analysis for the OS when at least 291 deaths have been observed, which is projected to occur approximately 24 months after study initiation. This formal comparison of OS will allow for early stopping for superiority and the stopping boundaries will be derived based on the actual number of deaths using O'Brien and Fleming α spending function in EAST v5.4. If the interim analysis is performed exactly at 291 OS events (76% of total events), the DMC can recommend to stop the study for superiority if the p-value was < 0.020. The nominal significance level for the final analysis after 382 OS events will be 0.044.

Secondary Endpoints and Analyses:

If superiority in OS is demonstrated at either interim or final analysis, a hierarchical hypothesis testing approach for the secondary endpoints of ORR and PFS will be used to preserve an overall type I error rate at 0.05 for efficacy claims. The secondary efficacy endpoints will be tested in the following hierarchical order: ORR first, then PFS.

ORR is defined as the proportion of all randomized subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) per RECIST 1.1 criteria. ORR will be compared using a two-sided 5% level Cochran-Mantel Haenszel (CMH) test stratified by the same stratification factors used for randomization. An associated odds ratio and 95% CI will be calculated. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson for each treatment arm. The difference in ORR between the two treatment arms along with the two-sided 95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factors.

PFS is defined as the time from randomization to the date of the first documented tumor progression (per RECIST 1.1 criteria) or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not have disease progression or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy. The distribution of PFS in two randomized arms will be compared using a two-sided, log-rank test stratified by the same stratification factors used for randomization. The HR and the corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each randomized arm will be estimated using the KM product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method.

The efficacy analyses methods for OS, ORR and PFS will also be evaluated in different subgroups, including squamous and non-squamous subgroups, PD-L1 positive and PD-L1 negative protein expression subgroups, and Chinese and non-Chinese subgroups. The analyses methods described above for OS, ORR and PFS will be repeated for each of the subgroups. However, the formal comparison between treatment groups will not be performed for these subgroups, ie, the stratified log-rank test for OS and PFS, and the CMH test for ORR described above.

Time to Treatment Failure (TTF) is defined as the minimum of the time from randomization to disease progression (RECIST 1.1 or Clinical), death or last dose date if a subject discontinued from treatment for any reasons other than "maximum clinical benefit" or "administrative reasons by sponsor". TTF is considered as event at the randomization date for subjects who were randomized but not treated. Clinical progression date is considered for time to treatment failure only when treatment is discontinued due to clinical disease progression. For nivolumab subjects treated beyond RECIST 1.1 progression, the event will be at RECIST 1.1 progression date. TTF is censored at the last dose date for subjects who discontinued treatment (without RECIST 1.1 progression) due to maximum clinical benefit or administrative reason by sponsor. TTF is censored at the last dose date for subjects who continued on treatment without progression or death. The distribution of TTF will be compared in the two randomized arms, using the first

~380 randomized subjects with minimum 8 months follow-up (TTF population), via a 1-sided, unstratified weighted log-rank test. The one-sided weighted log-rank p-value will be reported using G (rho = 0, gamma = 1) weights, in the terminology of Harrington and Fleming. The FH method (with rho = 0 and gamma = 1) leads to a loss of power when treatment effect is not delayed but has higher power when a delay of more than 2 months is observed, which is expected for TTF, based on data from global studies CheckMate 017 and 057. TTF will also be compared using a regular log rank test. The hazard ratio (HR) and the corresponding 1-sided 97.5% CI upper bound will be estimated in an unstratified Cox proportional hazards model using randomized arm as a single covariate. The TTF curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median will be constructed based on a log-log transformed CI for the survivor function S(t). The DMC will review the safety and efficacy data from the TTF interim analysis. There is no alpha spending nor penalty for TTF analysis: this interim analysis is considered as a bridging strategy. If TTF is statistically significant at 1-sided 0.025 level, safety and ORR will be described (no formal comparison) using the TTF population. TTR and DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) of the TTF population. Exposure and safety (including death summary) will be summarized on the Treated subjects among TTF population. Regardless of whether TTF is positive or negative, study will continue to the planned OS Interim/Final analysis.

Disease-Related Symptom deterioration Rate by Week 12 and by Week 24 is defined as the proportion of randomized subjects who had 10 points or more increase from baseline in Average Symptom Burden Index (ASBI) score at any time between randomization and Week 12/ Week 24 respectively. The disease-related symptom deterioration rates and corresponding 95% exact CIs will be calculated by Clopper-Pearson method for each randomized arm.

Safety Analyses:

Safety will be summarized and listed for all treated subjects using the NCI 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 v4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

Frequency, management and resolution of IMAEs will be analyzed. A tabular summary and comparative analysis between treatment arms of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-to onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE

Amendment 05 Update: Arm B subjects receiving docetaxel treatment at the time of Amendment 05 will continue to be monitored as specified in the protocol. They may continue to receive treatment with docetaxel or switch to nivolumab 3mg/kg given every 2 weeks.

TABLE OF CONTENTS

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1.2 Research Hypothesis

The treatment effect of nivolumab is consistent between the study population and subjects from global pivotal trials (CheckMate 057 and CheckMate 017) and nivolumab increases OS as

compared with docetaxel, in subjects with advanced or metastatic NSCLC who have failed prior platinum-based doublet chemotherapy.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To demonstrate that the OS benefit of nivolumab in this study population with advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy is consistent with benefit observed in global studies CheckMate 057 and CheckMate 017
- To compare the OS of nivolumab versus docetaxel in subjects with advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.

1.3.2 Secondary Objectives

- To compare the objective response rate (ORR) of nivolumab versus docetaxel.
- To compare the progression free survival (PFS) of nivolumab versus docetaxel.
- To compare the time to treatment failure (TTF) of nivolumab versus docetaxel
- To evaluate clinical efficacy (OS, ORR, and PFS) in different subgroups, including squamous and non-squamous NSCLC subgroups, PD-L1 positive and PD-L1 negative protein expression subgroups, and Chinese and non-Chinese subgroups.
- To evaluate rates of treatment related selected AEs and SAEs in nivolumab and docetaxel arms.
- To evaluate the proportion of subjects exhibiting disease-related symptom deterioration by Week 12 and by Week 24, as measured by LCSS, in nivolumab and docetaxel arms.

1.4.2.2 Docetaxel

Docetaxel (Taxotere®) is a cytotoxic microtubule inhibiting antineoplastic agent in the taxane class that is indicated as single agent treatment for locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel is recommended to be administered in a facility equipped to manage possible complications such as anaphylaxis. The dosing is recommended at 75 mg/m² administered intravenously over one hour on an every 3-week schedule. Per the Taxotere® label, the premedication regimen should be oral corticosteroids such

as dexamethasone at a dose of 8 mg BID for 3 days starting one day prior to administration and continued for one day after infusion.[87]

1.4.2.3 Safety of Docetaxel

The major adverse events related to docetaxel are primarily hematologic. The key Grade 3 to 4 hematologic toxicities include neutropenia (30 - 67%), anemia (2 - 5%) and thrombocytopenia (< 1 - 2%). Non-hematologic adverse events related to docetaxel include febrile neutropenia (4.7 - 12.7%), asthenia (47 - 55%), alopecia (35%), nausea (26 - 36%), diarrhea (12 - 36%), peripheral neuropathy (15 - 24%), vomiting (17%), and fluid retention (5 - 16%).[23,24,25,88,89] Warnings related to docetaxel include treatment-related mortality increases with abnormal liver function at higher doses, should not be given to subjects if the total bilirubin is greater than institutional upper limit of normal (ULN), or if AST and/or ALT is greater than 1.5x ULN concomitant with alkaline phosphatase greater than 2.5x ULN, should not be given if the neutrophil count of the subject is less than 1500 cell/mm³, should not be given if subjects have a history of severe hypersensitivity to docetaxel or drugs formulated with polysorbate 80, and may cause severe fluid retention.[87]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS 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.

[redacted]

2.2 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, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS 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.

2.3 Informed Consent

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 subject volunteers to participate.

BMS 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:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. 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.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator,

should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject'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 subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject 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.

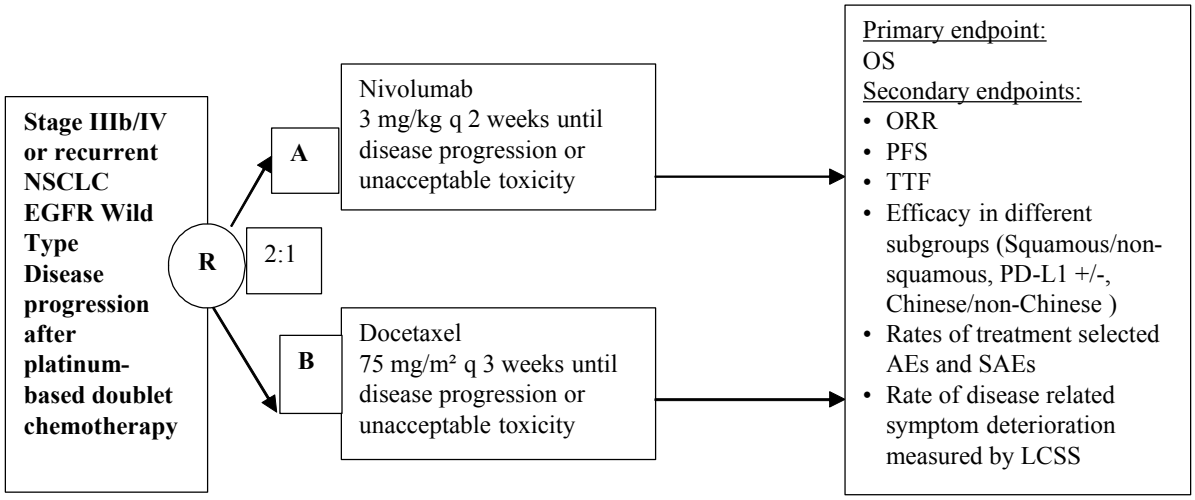
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, multinational randomized Phase 3 study in adult (≥ 18 years old) male and female subjects with advanced or metastatic NSCLC after failure of prior platinum-doublet chemotherapy. Subjects will undergo screening evaluations to determine eligibility prior to randomization. Subjects will be assigned to one of two treatment arms in a 2:1 ratio of nivolumab to docetaxel (see Study Design and Duration in Figure 3.1-1 below). Randomization will be stratified according to the following factors: histology (squamous vs non-squamous)/ PD-L1 Status (positive vs negative/ unevaluable)/ ECOG Performance status (0 vs 1). Approximately 100 PD-L1 unevaluable subjects will be randomized

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design



Treatment should be initiated within 3 business days of randomization. Nivolumab or docetaxel (depending on randomized treatment arm) will be administered as an IV infusion over 60 minutes on Treatment Day 1. A treatment cycle is defined as 2 weeks for nivolumab and 3 weeks for docetaxel.

Amendment 05 Update: The Data Monitoring Committee (DMC) for the CA209078 study convened on 21-Nov-2017 to evaluate the data from a planned formal Interim Analysis of overall survival (OS). The DMC declared superiority for OS in subjects receiving nivolumab as compared to docetaxel. As a result of the DMC assessment, this protocol amendment is being implemented to provide a mechanism for eligible subjects randomized to the docetaxel treatment Arm B to receive subsequent nivolumab therapy as part of a nivolumab crossover extension phase. In order to receive subsequent therapy with nivolumab, all subjects who received prior docetaxel and qualify for subsequent treatment with nivolumab, must sign an informed consent and will enter the nivolumab crossover extension phase of the study.

This study will consist of 3 phases: screening, treatment, follow-up in the original protocol and in the nivolumab crossover extension.

Screening for Original Study:

- Begins by establishing subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID.
- Tumor tissue (archival or recent tumor biopsy) must be available and received by the central lab for PD-L1 IHC testing for a subject to be randomized. Subjects must consent to allow the acquisition of tumor tissue by study personnel for performance of the correlative studies. (Table 5.1-1)
- EGFR mutation positive subjects (squamous or non squamous) are excluded from the study. Historical EGFR mutation status is accepted. If no historical EGFR status is available for non

squamous subjects, the test can be done locally or centrally using PCR as the recommended method. (IHC and VeriStrat testing are not qualified test methods. Other tests involving circulating tumor cell or DNA have not been validated and therefore are not acceptable methods). Non squamous subjects with unknown EGFR mutation status must be tested prior to randomization

- Baseline disease or tumor assessments should be performed within 28 days prior to randomization (according to Table 5.1-1).
- Subject is assessed for study eligibility within the required timeframe found in Table 5.1-1.

Treatment for Original Study:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to one of the treatment arms. Treatment should begin within 3 business days of randomization.
- All of the laboratories and vital signs will be collected within 3 calendar days prior to dosing of each cycle (according to Table 5.1-2 or Table 5.1-3). Adverse event assessments should be documented at each clinic visit.
- Biomarker, PK and immunogenicity samples will be done according to Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.5-1.
- Patient-reported outcome (PRO) instruments will be completed after randomization (prior to the first dose of study therapy), and prior to study procedures and dosing on Day 1 of each visit, according to Table 5.1-2 or Table 5.1-3.
- Study drug is administered as an IV infusion on Treatment Day 1 of each cycle (frequency is dependent on the treatment arm) until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.
- Subjects will be evaluated for response according to the RECIST 1.1 criteria. The first on treatment radiographic assessment will be obtained in both treatment arms at Week 6 (± 7 days). The subsequent radiographic assessments will be conducted every 6 weeks (± 7 days) for the first 12 months (Week 48), then every 12 weeks (± 14 days) until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent. Any subject who develops an objective tumor response per RECIST 1.1 (Complete Response or Partial Response) is required to undergo confirmatory scans at the next scheduled tumor assessment in the first year, and at least 4 weeks apart in the second and following year.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 for a complete list of reasons for discontinuation.

Follow-up for Original Study:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will be followed for drug related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication
- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 7 days) for the first 12 months

then every 12 weeks (± 14 days) until disease progression, lost to follow-up, withdrawal of study consent or death.
- After completion of the first two follow-up visits, subjects will be followed for overall survival every 3 months until death, lost to follow-up, or withdrawal of study consent.

PRO instruments will be completed at a frequency according to Table 5.1-4.

The total duration of the study from start of randomization to final analysis of OS is expected to be 37 months (11 months accrual + 26 months of follow-up).

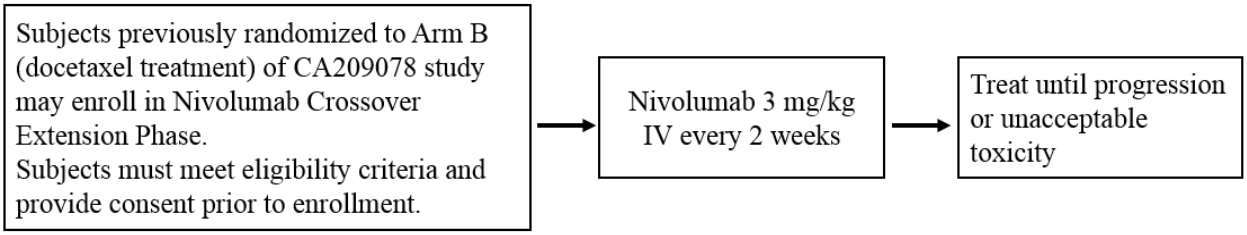
This study will end when survival follow-up is complete. The current plan is to continue survival follow-up for approximately 5 years after the last subject's first visit.

Amendment 05 Update for Nivolumab Crossover Extension

Screening for Nivolumab Crossover Extension

- Subjects currently receiving treatment with nivolumab (Arm A) will continue to be treated and monitored as specified in the protocol.
- With Amendment 05, all subjects randomized to docetaxel treatment (Arm B) who meet eligibility criteria may enter the Nivolumab Crossover Extension Phase, according to the schema in Figure 3.1-2. These subjects will follow the assessment schedules outlined in Table 5.1-5 of the protocol.
- Subjects treated with docetaxel who have ended study treatment will be able to receive treatment with nivolumab via the crossover extension phase of the study, assuming basic inclusion/exclusion criteria are met (including a 3-week washout period for prior systemic anti-cancer therapy). Details are provided in Section 3.3.1.1 and Section 3.3.2.1.
- Subjects currently receiving treatment with docetaxel should continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from docetaxel in the judgment of the investigator. These subjects may receive nivolumab once they are discontinued from docetaxel therapy, assuming basic inclusion/exclusion criteria are met (including a 3-week washout period from last dose of docetaxel).

Figure 3.1-2: Nivolumab Crossover Extension Phase Schema for Subjects Previously Randomized to Docetaxel



Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.5.4. Treatment beyond progression for subjects in the nivolumab crossover extension phase must be approved by the BMS Medical Monitor prior to subjects receiving additional study drug. Criteria for discontinuation of treatment beyond progression are described in Section 4.5.4. Subjects who discontinue study therapy for reasons other than progression should continue to be scanned until disease progression is documented.

Treatment for Nivolumab Crossover Extension:

- Begins with the call to the IVRS. The subject is assigned to the Nivolumab Crossover Extension Phase. Treatment should begin within 3 business days of crossover.
- All of the laboratories and vital signs will be collected within 3 calendar days prior to dosing of each cycle (according to Table 5.1-6). Adverse event assessments should be documented at each clinic visit.
- Patient-reported outcome (PRO) instruments will be completed after enrollment (prior to the first dose of study therapy), and prior to study procedures and dosing on Day 1 of each visit, according schedule in Table 5.1-5.
- Nivolumab is administered as an IV infusion on Treatment Day 1 of each cycle until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.
- Subjects will be evaluated for response according to the RECIST 1.1 criteria. The first on treatment radiographic assessment will be obtained in both treatment arms at Week 6 (± 7 days). The subsequent radiographic assessments will be conducted every 6 weeks (± 7 days) for the first 12 months (Week 48), then every 12 weeks (± 14 days) until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent. Any subject who develops an objective tumor response per RECIST 1.1 (Complete Response or Partial Response) is required to undergo confirmatory scans at the next scheduled tumor assessment in the first year, and at least 4 weeks apart in the second and following year.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 for a complete list of reasons for discontinuation.

Follow-up for Nivolumab Crossover Extension:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will be followed for drug related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication. Two follow-up visits for safety within the first 100 days from the last dose of nivolumab therapy are included according to Table 5.1-7 and Section 5.3.
- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 7 days) for the first 12 months then every 12 weeks (± 14 days) until disease progression, lost to follow-up, withdrawal of study consent or death.
- After completion of the first two follow-up visits, subjects will be followed for overall survival every 3 months until death, lost to follow-up, or withdrawal of study consent.

PRO instruments will be completed at a frequency according to Table 5.1-7.

This study will end when survival follow-up is complete. The current plan is to continue survival follow-up for approximately 5 years after the last subject's first visit.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug consistent with the original study drug assignment Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects 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 subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2. Target Population

a) ECOG performance status of ≤ 1 (see Appendix 1).

b) Subjects with histologically- or cytologically-documented NSCLC who present with Stage IIIB/ Stage IV disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).

c) Subjects must have experienced disease progression during or after one prior platinum-containing doublet chemotherapy (carboplatin or cisplatin) regimen for advanced or metastatic disease.

i) Subjects who received maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and progressed are eligible

ii) Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.

iii) Subjects with recurrent disease > 6 months after platinum containing adjuvant, neoadjuvant or definite chemoradiation therapy given for locally advanced disease,

who also subsequently progressed during or after a platinum- doublet regimen given to treat the recurrence, are eligible.

d) Subjects have measurable disease by CT or MRI per RECIST 1.1 criteria (per Appendix 2); Radiographic Tumor Assessment performed within 28 days prior to randomization.

   i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.

e) A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 10 unstained slides (submission of less than 10 unstained slides may be acceptable after approval by BMS Medical Monitor) of tumor sample (archival or recent) must be available for biomarker evaluation at a central laboratory, as described in Section 1.1.1. In order to be randomized, subjects will be classified as PD-L1 positive, PD-L1 negative or PD-L1 unevaluable. Biopsy should be excisional, incisional or core needle. Fine beedle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable

f) All baseline laboratory requirements will be assessed and should be obtained within 14 days prior to randomization. Screening laboratory values must meet the following criteria

   i) WBCs $\geq 2000/\mu L$
   ii) Neutrophils $\geq 1500/\mu L$
   iii) Platelets $\geq 100 \times 10^3/\mu L$
   iv) Hemoglobin ≥ 9.0 g/dL
   v) Serum creatinine of $\leq$ 1.5 X ULN or creatinine clearance $>$ 40 mL/minute (using Cockcroft/Gault formula)

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

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

   vi) AST $\leq$ 1.5X ULN
   vii) ALT $\leq$ 1.5X ULN
   viii) Total bilirubin $\leq$ ULN
   ix) Alkaline phosphatase $\leq$2.5 X ULN

g) Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to randomization. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to randomization

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

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 5 half-lives of Nivolumab plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion (for subjects in Arm A).

WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment with Docetaxel plus 5-half lives of Docetaxel plus 30 days (duration of ovulatory cycle) for a total of 33 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in Arm B)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with Nivolumab plus 5 half-lives of the Nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with Docetaxel plus 5 half-lives of Docetaxel 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 (for subjects treated in Arm B

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

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

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*
  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

LESS EFFECTIVE METHODS OF OF CONTRACEPTION

- Male condoms with spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.
  * A male and female condom must not be used together

UNACCEPTABLE METHODS OF CONTRACEPTION

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

3.3.1.1 Inclusion Criteria for Entering the Nivolumab Crossover Extension Phase-Subjects Previously Randomized to Docetaxel

4. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form for the nivolumab crossover extension phase in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any nivolumab crossover extension protocol-related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the nivolumab crossover extension phase.

5. Target population

a) Patients previously randomized to Docetaxel Treatment Arm B on the CA209078 study.

b) Prior systemic anti-cancer therapy, including docetaxel must have been completed at least 3 weeks prior to first dose of nivolumab administration. Prior radiotherapy must have been completed at least 2 weeks prior to first dose of nivolumab administration.

c) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 or baseline before administration of first dose of nivolumab.

d) Subjects with asymptomatic brain metastases are eligible. Subjects with symptomatic CNS metastases are eligible if CNS metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first dose of nivolumab administration. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

e) Laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose of nivolumab:

i) WBC ≥ 2000/µL

ii) Neutrophils ≥ 1500/µL

iii) Platelets ≥ 100x103/µL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤1.5 x ULN or creatinine clearance

(CrCl) > 40 mL/min (using the Cockcroft/Gault formula):

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

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

vi) AST/ALT ≤ 3.0 x ULN

vii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3`.0 mg/dL).

f) ECOG performance status 0-1

6. Age and Reproductive Status

See Section 3.3.1 3) Age and Reproductive Status

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with carcinomatous meningitis.

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

c) Subjects with EGFR mutation regardless of mutation type are excluded. Non squamous subjects with unknown EGFR mutation status must be tested for EGFR mutation (use of PCR based test is strongly encouraged). If the EGFR mutation is positive, subject is excluded.

d) Subjects with known ALK translocation are excluded.

2. Medical History and Concurrent Diseases

a) Subjects with an active, known or suspected autoimmune disease are excluded. Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorder (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.

b) Subjects 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.

c) Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.

d) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

e) Not applicable

f) Prior treatment with docetaxel.

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

h) Other active malignancy requiring concurrent intervention.

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

j) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0) or baseline before administration of study drug.

k) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days prior to randomization.

l) Active Tuberculosis (TB) infection based on chest X-ray, sputum tests, and clinical examination. Patients with a history of active TB infection within last 1 year are excluded even if it was treated; Patients with a history of active TB infection greater than 1 year

ago are eligible if there is no evidence of active TB in current status in the investigator's opinion.

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

n) EGFR wild-type subjects who received EGFR inhibitor as prior systemic anti-cancer therapy are excluded. Subjects without ALK translocation who received ALK inhibitor as prior systemic anti-cancer therapy are exclude.

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

3. Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus antibody (HCV Ab) indicating acute or chronic infection.

c) Subjects with ≥ Grade 2 peripheral neuropathy

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of severe hypersensitivity reaction to prior paclitaxel.

c) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

b) Subjects 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 subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.2.1 Exclusion Criteria for Entering the Nivolumab Crossover Extension Phase-Subjects Previously Randomized to Docetaxel

6. Medical History and Concurrent Diseases

a) Subjects with active, known or suspected autoimmune disease. Subjects 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 in nivolumab crossover extension phase

b) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within

14 days prior first dose of nivolumab administration. Corticosteroids with minimal systemic absorption (for example topical, inhalational, or as specified in Section 3.4.3), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

c) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of nivolumab administration

d) Prior treatment with an anti-PD-1 or anti-PD-L1 therapy.

e) Subjects with carcinomatous meningitis

f) Other active malignancy requiring concurrent intervention

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

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

7. Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

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

8. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions

9. Other Exclusion Criteria

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

b) Prisoners or subjects who are involuntarily incarcerated

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

Eligibility criteria for the Nivolumab Crossover Extension Phase have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause 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 > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

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

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Strong CYP3A4 inhibitors should be avoided for subjects in Arm B (docetaxel) during the study (refer to docetaxel package insert for details). This includes (but is not limited to):

3.4.1.1 Strong CYP3A4 inhibitors

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanavir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

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 this Section 3.4.3).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy (including but not limited to thymosin, interleukine-2), extensive, non-palliative radiation therapy, standard or investigational agents for treatment of NSCLC).

Except for the permitted procedures specified as palliative local therapies (Section 3.4.3.1), all other radiation therapy or surgery to any tumor lesion is not permitted during study treatment. Subjects who require such non-palliative procedures must be discontinued from study treatment

3.4.2 Other Restrictions and Precautions

Subjects randomized to Arm B (docetaxel) should refrain from excessive consumption of grapefruit, seville oranges, and products/juices made with these fruit.

Subjects 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

3.4.3 Permitted Therapy

Subjects 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 Physiologic replacement doses of systemic corticosteroids (eg, prednisone ≤ 10 mg/day) 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.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates) is allowed. RANK-L inhibitors are not allowed during study treatment. Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization.

3.4.3.1 Palliative local therapy

Palliative local therapy, including palliative radiation therapy- and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study treatment for subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study treatment in subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the BMS Medical Monitor.

Subjects requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects in Arm A (Nivolumab) must either discontinue nivolumab or they must meet criteria to continue nivolumab treatment beyond progression (Section 4.5.4) in order to resume nivolumab after palliative local therapy. Subjects in Arm B (Docetaxel) who are found to have progression per RECIST 1.1 on any tumor assessments prior to the initiation of palliative local therapy must discontinue chemotherapy.

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

3.5 Discontinuation of Subjects Following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- 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 subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specific reasons for discontinuation (See Section 4.5.5).

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject 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 drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days

from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all *randomized* subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects 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 drug 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 subject 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.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the 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 subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

Table 4-1: Study Drug for CA209078					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open Label**	**Packaging/Appearance**	**Storage Conditions (per label)**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open Label	10 mL vial/ 5 vials per carton Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° to 8°C. Protect from light and freezing.
Docetaxel Concentrate for solution for infusion	160 mg (20 mg/ mL)[a]	IP	Open Label	8 mL vial/ 1 vial per carton Pale yellow to brownish yellow solution	Do not store above 25°C. Store in original package and Protect from light.
Docetaxel Concentrate for solution for infusion	20 mg (40 mg/ mL)	IP	Open Label	2 vials per carton (1 vial of 20mg/0.5mL concentrate for solution + 1 vial of solvent) Clear viscous, yellow to brown-yellow solution	Do not store above 25°C. Store in original package and Protect from light.
Dexamethasone Tablets	4 mg[a]	Non-IP	N/A	Wallet (blister) card of 20 tablets Scored tablets	Store at 15° - 25° C.

**Medications used to treat nivolumab-related infusion reactions are (eg diphenhydramine, acetaminophen/paracetamol, corticosterioids) considered NIMPs (noninvestigational products) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert or summary of product characteristics (SmPC). For further details related to these medications and nivolumab-related infusion reactions, please see Section 4.5.6.

[a] For sites/countries in which investigative site staff will procure locally marketed product, the potency/packaging size may differ based on the locally available product

4.1 Investigational Product

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.

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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

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

- Nivolumab
- Docetaxel

Docetaxel will be provided by BMS as listed in Table 4-1 for certain countries and may be procured by the investigative sites in other countries as local commercial product, where allowed by local regulations. The sites will also procure IV bags, diluents, and micron in-line filters (ie, 0.2/ 1.2 micron; see current Nivolumab Investigator Brochure for required filter details).

4.2 Non-investigational Product

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.

In this protocol, non-investigational product(s) is/are: Dexamethasone (for 3 days in the docetaxel arm only as premedication), and any medications used to treat nivolumab related infusion reactions (see Section 4.5.6).

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug 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 drug arise, the study drug should not be dispensed and contact BMS immediately.

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).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Nivolumab vials must be stored in the refrigerator at 2 - 8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Docetaxel and dexamethasone should be stored according to the market product package insert or clinical label.

Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

After Nivolumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current Nivolumab Investigator Brochure.[22]

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60 minute IV infusion. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) and administration will be found in the pharmacy reference sheet and/or the current Investigator brochure for nivolumab.[22]

For sites utilizing the docetaxel 160 mg, 20 mg vials provided by Bristol-Myers Squibb, the preparation instructions found within the current SmPC (or equivalent document) should be followed.[92]

For sites utilizing locally-sourced docetaxel, please follow storage and administration instructions on the package insert or SmPC.[89,92]

4.4 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth.

Once enrolled in IVRS, enrolled subjects that have signed informed consent and met all eligibility criteria will be ready to be randomized through the IVRS, upon confirmation of receipt

of required tissue sample by the central lab. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Date of informed consent
- Histology (squamous vs non-squamous) : Subjects with mixed histology should be classified according to the predominant histology. Subjects with adenosquamous histology should be classified as non-squamous histology
- ECOG Performance status (0 vs 1)
- PDL-1 Status

Subjects meeting all eligibility criteria and randomized onto the study will be assigned in a 2:1 ratio into one of the two treatment arms, and stratified by the following factors: histology (squamous vs non-squamous)/ PD-L1 Status (positive vs negative/ unevaluable)/ ECOG Performance status (0 vs 1). The randomization will be carried out via permuted blocks within each stratum.

Amendment 05 Update: IVRS will be amended to allow all subjects previously randomized to Arm B (docetaxel treatment) to receive treatment with nivolumab. The IVRS will assign the nivolumab treatment for all subjects eligible for the Nivolumab Crossover Extension Phase. Procedural information will be provided in a separate document.

Subjects currently randomized to Arm B (docetaxel treatment) may continue docetaxel treatment previously through the IVRS, as long as subjects continue to derive benefit from docetaxel in the judgment of the investigator.

4.4.1 Treatment Arms

Arm A: Nivolumab and Nivolumab Crossover Extension Phase

No premedications are recommended for initiation of dosing.

Arm B: Docetaxel

Dexamethasone 8 mg PO BID (or institutional equivalent) on the day before, day of, and day after chemotherapy. Please use the institutional standard for dexamethasone dosing.

4.5 Selection and Timing of Dose for Each Subject

Nivolumab

Subjects randomized to Arm A (the experimental arm) and enrolled in Nivolumab Crossover Extension Phase will receive treatment with nivolumab as a 60 minute IV infusion, on Day 1 of a treatment cycle every 2 weeks. Dosing calculations should be based on the body weight assessed at the start of each cycle as per Table 5.1-2 or Table 5.1-6 for Nivolumab Crossover Extension Phase. If the subject's weight on the day of dosing differs by > 10% from the weight used to

calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of nivolumab allowed.

Subjects may be dosed no less than 12 days from the previous dose and no more than 3 days from the scheduled dose. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6.

Docetaxel

Subjects randomized to Arm B (the control arm) will receive treatment with docetaxel as a 60 minute IV infusion on Day 1 of a treatment cycle every 3 weeks. Dosing calculations should be based upon the body surface area calculation assessed as per Table 5.1-3. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. Dose modifications for toxicity will be performed according to Section 4.5.2.2. Subjects may be dosed no less than 19 days from the previous dose and no more than 3 days from the scheduled dose.

On both arms and Nivolumab Crossover Extension Phase, treatment may be delayed for up to a maximum of 6 weeks from the last dose (see Section 4.5.3).

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria.

4.5.1 Dose Delay Criteria

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

4.5.1.1 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 amylse or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see 4.5.5.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

4.5.1.2 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 cells/mm^3
  - Should not be given if total bilirubin > upper limit of normal (ULN), or if AST and/or ALT > 1.5xULN concomitant with alkaline phosphatase > 2.5x 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 4.5.2.2.

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

4.5.2 Dose Reductions

4.5.2.1 Nivolumab Dose Reductions

There will be no dose reduction for nivolumab.

4.5.2.2 Docetaxel Dose Reductions

Dose reductions of docetaxel may be required,[87] and will be performed according to Table 4.5.2.2-1.

Table 4.5.2.2-1: Dose Reductions of Docetaxel

Dose Level	Docetaxel
Starting dose	75 mg/m^2
First dose reduction	55 mg/m^2
Second dose reduction	37.5 mg/m^2
Third dose reduction	Discontinue docetaxel

Doses of docetaxel will be modified for subjects who experience any of the following conditions during docetaxel treatment:

- Febrile neutropenia (body temperature ≥ 38.5 C and neutrophils < 1,000 cell/mm3)
- Neutrophils < 500 cell/mm³ for more than one week despite growth factor support
- Severe or cumulative cutaneous reactions

- Other Grade 3/4 non-hematological toxicities.

Subjects should have treatment delayed according to Sections 4.5.1.2 and 4.5.2.2, and then resumed at one dose level reduction (55 mg/m^2). Should these AEs occur after the first dose reduction, then a second dose reduction to 37.5 mg/m^2 is permitted. If a third dose reduction is required, then the subject should discontinue docetaxel treatment and enter the follow-up phase.

Subjects who develop Grade ≥ 3 peripheral neuropathy, or who otherwise meet criteria specified in Section 4.5.5.2, should discontinue docetaxel treatment and enter the follow-up phase.

4.5.3 Criteria to Resume Dosing

4.5.3.1 Criteria to Resume Treatment with Nivolumab

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects 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.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5.1) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects 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.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation of control with hormone replacement.
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.1.

4.5.3.2 Criteria to Resume Treatment with Docetaxel

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

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

- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5.2) should have treatment permanently discontinued

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.2.

When resuming docetaxel treatment, please follow the dose reduction recommendations noted in Section 4.5.2.2.

4.5.4 Treatment Beyond Disease Progression

As described in Section 1.4.3.3, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects treated with docetaxel (Arm B) will not be permitted to continue their treatment beyond initial RECIST 1.1 defined PD.

Subjects treated with nivolumab (Arm A and Nivolumab Crossover Extension Phase) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Tolerance of study drug
3. Stable performance status
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5. Subject provides written informed consent prior to receiving additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the BMS medical Monitor and documented in the study records.

A radiographic assessment/ scan should be performed within 6 weeks (± 7 days) of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on Table 5.1-2 or Table 5.1-6 for Nivolumab Crossover Extension Phase.

For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

For subjects in both treatment arms and the Nivolumab Crossover Extension Phase, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as « symptomatic » deterioration. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation from study treatment.

4.5.5 Treatment Discontinuation Criteria

Tumor assessments for all subjects should continue as specified in Section 5.4.1 even if dosing is discontinued.

4.5.5.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

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

    * In most cases of Grade 3 AST or ALT elevation, study 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
- 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 amylse 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.
- Creatinine > 6x ULN
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 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 subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

4.5.5.2 Docetaxel Dose Discontinuation

Docetaxel treatment should be permanently discontinued for the following:

- Any 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) abnormality 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 or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia
  - Grade 4 lymphopenia or leukopenia
  - 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
- Any dosing delay lasting > 6 weeks with the following exceptions:
  - Dosing delay > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued docetaxel dosing.

4.5.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is 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, arthalgias, 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 4.0) guidelines.

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

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject 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 subject 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 SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject 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. Subject 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 subject 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).

4.5.7 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered immuno-oncology agents in this protocol. Early recognition and management of adverse events 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 adverse events: gastrointestinal, renal, pulmonary, pancreatitis, hepatic, endocrinopathies, skin and neurological. The management algorithms can be found in the Nivolumab investigator brochure and Appendix 3 of this protocol.

4.6 Blinding/Unblinding

Not applicable.

An open-label (rather than blinded) study design was selected because the management of similar AEs will differ between treatment arms, given the different mechanisms of action of docetaxel and nivolumab. Different dose modification rules (no dose reductions for nivolumab vs allowance for dose reductions for docetaxel) and different drug-drug interaction profiles add complexity to any blinding strategy.

Subjects have potentially different AEs, as nivolumab has shown immune-related events while docetaxel has an adverse event profile that consists primarily of hematologic events. Although both drugs have been noted to cause pulmonary AEs, these events are treated differently. With docetaxel, pulmonary AEs are mainly due to neutropenic fever and pneumonia, requiring broad-spectrum antibiotics and growth factors. With nivolumab, pulmonary AEs are immune related and are treated with systemic steroids. If this trial is blinded, the management of AEs would potentially be delayed or detrimental to the subject.

4.7 Treatment Compliance

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

4.8 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

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

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments and Procedures (CA209078) For ARMS A and B

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to randomization.
Medical History	X	
Review Prior Cancer treatment	X	
Safety Assessments		
Vital Signs and oxygen saturation	X	• Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest. • Obtain vital signs at screening visit and within 72 hours prior to first dose.
Physical examination and physical measurements (including Performance Status)	X	Includes Height and Weight, and ECOG status within 28 days prior to first dose
Laboratory Tests	X	Labs performed locally within 14 days prior to randomization: • CBC with differential • Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, amylase and lipase) • AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, • TSH, free T3, free T4, • HepB/C (HBV sAg, HCV Ab) within 28 days prior to randomization • HIV testing only if no known history for testing result (per local requirement)
Pregnancy Test	X	Performed within **24** hours prior to first dose (serum or urine for WOCBP only).

Table 5.1-1: Screening Assessments and Procedures (CA209078) For ARMS A and B		
Procedure	**Screening Visit**	**Notes**
ECG (12-Lead)	X	
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose.
Concomitant Medication collection	X	Within 14 days prior to first dose.
Efficacy Assessments		
Radiographic Tumor Assessment (Chest, abdomen, pelvis, brain)	X	• Should be performed within 28 days prior to randomization. • CT/MRI of brain (with contrast) should be performed to rule out brain metastases. (Brain MRI is preferred) • Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy (for IHC)	X	May be archival or recent sample. 1 formalin-fixed paraffin embedded tumor tissue block, or minimum of 10 FFPE unstained slides are needed. Submission of fewer than 10 unstained slides may be acceptable under certain circumstances and must be approved by BMS Medical Monitor PD-L1 result will be assessed prior to randomization and will be used as stratification factor (PD-L1 positive vs PD-L1 negative/unevaluable)
EGFR Mutation Status	X	To be available prior to randomization for non squamous subjects. Historical results is acceptable. EGFR mutant subjects are excluded.
IVRS / CLINICAL DRUG SUPPLIES		
IVRS	X	For subject number assignment at the time informed consent is obtained.

Table 5.1-2: On-Study Assessments ARM A (NIVOLUMAB)					
Procedure	**Cycle 1 Day 1**	**Each cycle (every 2 weeks) on Day 1 (± 3 days)**	**Every other cycle (every 4 weeks) on Day 1 (± 5 days)**	**Every 3 cycles (6 weeks ± 5 days)**	**Notes (add note on cycles)**
Safety Assessments					
Vital Signs and oxygen saturation	X	X			Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 3 calendar days prior to dosing and at any time a subject has any new or worsening respiratory symptoms..
Physical examination and physical measurements (including Performance Status)	X	X			Includes Weight and ECOG status.
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------Continuously----------				Assessed using NCI CTCAE v. 4.0.
Laboratory Tests	X	X			Within 3 calendar days prior to dosing and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH Note: Cycle 1 Day 1 labs do not need to be repeated if they were performed within 14 days prior to 1st dose
Thyroid Function Testing	X			X	TSH (reflex to free T3 and free T4 if abnormal result). Note: Cycle 1 Day 1 labs do not need to be repeated if they were performed within 14 days prior to 1st dose
Pregnancy Test	X		X		Serum or urine (for WOCBP only) test to be performed within 24 hours prior to first dose and **every 4 weeks (±1 week)** regardless of dosing schedule.

Table 5.1-2: On-Study Assessments ARM A (NIVOLUMAB)					
Procedure	**Cycle 1 Day 1**	**Each cycle (every 2 weeks) on Day 1 (± 3 days)**	**Every other cycle (every 4 weeks) on Day 1 (± 5 days)**	**Every 3 cycles (6 weeks ± 5 days)**	**Notes (add note on cycles)**
Review of Concomitant Medications	continuously				Review at every visit.
Efficacy assessments					
Radiographic Tumor Assessment	• FIRST tumor assessment should first be performed at 6 weeks (± 7 days) from randomization date. SUBSEQUENT tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months, then every 12 weeks (+-- 14 days) until disease progression (or discontinuation of study medication for subjects treated beyond radiographic progression). • Subjects with a history of brain metastasis should have surveillance MRI every 6 weeks, or sooner if clinically indicated. • Assessments should include chest, pelvis and abdomen (with contrast) as well as any area that is being monitored. • Follow RECIST 1.1 criteria				
Biomarker					
Serum (for soluble factors and miRNA Analyses)	X			X	• Must be obtained any time after randomization (prior to dosing) at Cycle 1 Day 1, then every 6 weeks. • If dose is delayed, serum samples are not taken and are delayed until dose is resumed
Whole Blood (for SNP testing)	X				Can be obtained on Day -3 to Day 1 prior to dosing.
Pharmacokinetic and Immunogenicity Assessments (nivolumab Treatment Arm ONLY)	---------- Throughout study ----------				For detailed sample timing, see Table 5.5-1 in this section. **Amendment 05 Update: As of Amendment 05,** PK/immunogenicity will not be collected.

Table 5.1-2: On-Study Assessments ARM A (NIVOLUMAB)					
Procedure	**Cycle 1 Day 1**	**Each cycle (every 2 weeks) on Day 1 (± 3 days)**	**Every other cycle (every 4 weeks) on Day 1 (± 5 days)**	**Every 3 cycles (6 weeks ± 5 days)**	**Notes (add note on cycles)**
Outcome Research assessments					
Patient reported outcomes (PRO) Assessment	X		X		• **For Cycle 1Day 1**- performed after randomization PRIOR to first dose (day -3 to +1). • **For on study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. • Assessments will be performed at every other cycle on Day 1 (+/- 5 days) for the first 6 months on study, then every 6 weeks thereafter for the remainder of the study.
Health Care Resource Utilization		X			• **Except Cycle 1 (Day 1)**
Clinical Drug Supplies					
Nivolumab (3mg/kg)	X	X			• Cycle 1 Day 1 dose must be administered within 3 business days of randomization • Record Study Drug Infusion start and stop times. Note: Continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)				
Procedure	**Cycle 1 Day1**	**Each cycle (every 3 weeks) on Day 1 (± 3 days)**	**Every 2 cycles (6 weeks ± 5 day)**	**Notes (add note on cycles)**
Safety Assessments				
Vital Signs and oxygen saturation	X	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 3 calendar days prior to dosing and at any time a subject has any new or worsening respiratory symptoms..
Physical examination and physical measurements (including Performance Status)	X	X		Includes Weight (calculated BSA) and ECOG status.
Adverse Events (AE) and Serious Adverse Event (SAE)Assessment	----------Continuously----------			Assessed using NCI CTCAE v. 4.0.
Laboratory Tests	X	X		Within 3 calendar days prior to dosing and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH Note: Cycle 1 Day 1 labs do not need to be repeated if they were performed within 14 days prior to 1st dose
Thyroid Function Testing	X		X	TSH (reflex to free T3 and free T4 if abnormal result) Note: Cycle 1 Day 1 labs do not need to be repeated if they were performed within 14 days prior to 1st dose
Pregnancy Test	X		X	Serum or urine (for WOCBP only) test to be performed within 24 hours prior to first dose and **every 4 weeks (±1 week)** regardless of dosing schedule.
Review of Concomitant Medications	Continuously			Review at every visit

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)				
Procedure	**Cycle 1 Day1**	**Each cycle (every 3 weeks) on Day 1 (± 3 days)**	**Every 2 cycles (6 weeks ± 5 day)**	**Notes (add note on cycles)**
Efficacy Assessment				
Radiographic Tumor Assessment	• FIRST tumor assessment should first be performed at 6 weeks (± 7 days) from randomization date. SUBSEQUENT tumor assessments should occur every 6 weeks (± 7 days) up to first 12 months, then every 12 weeks until disease progression. • Subjects with a history of brain metastasis should have surveillance MRI every 6 weeks, or sooner if clinically indicated. • Assessments should include chest, pelvis and abdomen (with contrast) as well as any area that is being monitored. • Follow RECIST 1.1 criteria			
Biomarker				
Serum (for soluble factors and miRNA Analyses)	X		X	• Must be obtained any time after randomization (prior to dosing) at Cycle 1 Day 1, then every 6 weeks. • If dose is delayed, serum samples are not taken and are delayed until dose is resumed
Whole Blood (for SNP testing)	X			Can be obtained on Day -3 to Day 1 prior to dosing
Outcome Research assessments				
Patient reported outcomes (PRO) Assessment	X	X		• **For Cycle 1 Day 1**- performed after randomization PRIOR to first dose (day -3 to +1). • **For on-study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. • Assessments will be performed at every cycle on Day 1 (± 5 days) for the first 6 months on study, then every 6 weeks thereafter for the remainder of the study.
Health Care utilization		X		• Except Cycle 1 Day 1

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)				
Procedure	**Cycle 1 Day1**	**Each cycle (every 3 weeks) on Day 1 (± 3 days)**	**Every 2 cycles (6 weeks ± 5 day)**	**Notes (add note on cycles)**
Clinical Drug Supply				
Docetaxel (75mg/m^2)	X	X		• Cycle 1 Day 1 dose must be administered within 3 business days of randomization • Record Study Drug Infusion start and stop times. • Dexamethasone 8mg PO BID (or institutional equivalent) on the day before, day of, and day after chemotherapy. Please use the institutional standard for dexamethasone dosing. Note: continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure

Table 5.1-4: Follow-up and Survival Procedures (CA209078) For ARM A and B			
Procedure	**Follow-up Visits 1 (X01) and 2 (X02)[a]**	**Further Follow-up Phase (beyond X02)[b]**	**Notes**
Radiographic Tumor Assessment	• For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed every 6 weeks (± 7 days) up to the first 12 months, then every 12 weeks (± 14 days) until PD, withdrawal of consent, lost to follow-up or death. • Radiographic assessments for subjects who have not experienced PD ***must*** be obtained every 6 weeks (±7 days), and ***not*** delayed until X01 or X02.		
Outcome Research Assessments			
Patient reported outcomes (PRO) Assessment	X	EQ5-D Only	Both the LCSS and EQ-5D will be given in FU Visits 1 & 2. In Survival Visits, the EQ-5D will be collected every 3 months for the first year of the Survival Phase, then every 6 months thereafter
Healthcare resource utilization	X		
Safety assessment			
Adverse Events (AE) and Serious Adverse Event (SAE)Assessment	X	X*	* beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent anti cancer therapy
Laboratory Tests	X		• At First follow-up visit (X01) only • CBC with differential. • Serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), LDH. • AST, ALT, total bilirubin, alkaline phosphatase, amylase, lipase. • TSH (reflex to free T3 and free T4 if abnormal result) Note: Repeat at Visit 2 only of study drug toxicity persists
Pregnancy test	X		
Review of Concomitant Medications	X		

Table 5.1-4: Follow-up and Survival Procedures (CA209078) For ARM A and B			
Procedure	**Follow-up Visits 1 (X01) and 2 (X02)[a]**	**Further Follow-up Phase (beyond X02)[b]**	**Notes**
Collection of Survival Status Information	X	X	Every 3 months (+/- 14 days) in Survival visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit to update survival information and assess subsequent anti-cancer therapy

[a] Follow up visit 1 to occur 35 days from the last dose (± 7 days). Follow up visit 2 to occur 80 days (± 7 days) from Follow-up visit 1

[b] First Survival visit to occur 3 months (± 14 days) from Follow-up visit 2

Table 5.1-5: Screening Assessments and Procedures (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase		
Procedure	**Screening Visit**	**Notes**
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to calling IVRS and registering subject for crossover extension phase
Medical History	X	
Safety Assessments		
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, RR, O^2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen, if applicable). Obtain vital signs w/in 72 hrs of first dose of nivolumab
Physical Measurements (including Performance Status)	X	Includes Height and Weight, and ECOG status within 28 days prior to first dose of nivolumab Focused physical exam may be performed at screening, if clinically indicated
Laboratory Tests	X	Labs performed locally within 14 days prior to first dose of Nivolumab (unless otherwise specified): CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), amylase, lipase, AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4
Pregnancy Test	X	Performed within **24** hours prior to first dose of nivolumab (serum or urine for WOCBP only)
ECG (12-Lead)	X	
Assessment of signs and symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose of nivolumab
Concomitant Medication collection	X	Within 14 days prior to first dose of nivolumab
Efficacy Assessments		
Radiographic Tumor Assessment (Chest, abdomen, pelvis, brain)	X	Should be performed within 28 days prior to first dose of nivolumab. CT/MRI of brain (with contrast, unless contraindicated) is required in subjects with a known history of brain metastases (brain MRI is preferred). Additional sites of known or suspected disease (including CNS) should be imaged prior to first dose of nivolumab and at subsequent study assessments.

Table 5.1-6: On-Study Assessments (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase

Procedure	F1D1	Each cycle on Day 1 (± 3 days)	Every 3 cycles on Day 1 (± 3 days)	Every 6 cycles on Day 1 (± 3 days)	Notes 3mg/kg dosing cycle = 2 Weeks
Safety Assessments					
Vital Signs and Oxygen saturation	X	X			Within 72 hours prior to dosing: temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------continuously----------				Assessed using NCI CTCAE v. 4.0
Physical examination and physical measurements (including Performance Status)	X	X			Includes Weight and ECOG status
Complete blood counts(CBCs) (Results obtained prior to dosing on infusion days)	X	X			Screening labs performed within 7 days of F1D1 visit do not need to be repeated unless clinically indicated. For F2D1 and beyond, to be performed within 72 hours prior to dosing, tests include WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests (Results obtained prior to dosing on infusion days)	X	X			Screening labs performed within 7 days of F1D1 visit do not need to be repeated unless clinically indicated. For F2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), LDH
Liver Function Testing (Results obtained prior to dosing on infusion days)	X	X			Screening labs performed within 7 days of F1D1 visit do not need to be repeated unless clinically indicated. For F2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1-6: On-Study Assessments (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase					
Procedure	**F1D1**	**Each cycle on Day 1 (± 3 days)**	**Every 3 cycles on Day 1 (± 3 days)**	**Every 6 cycles on Day 1 (± 3 days)**	**Notes 3mg/kg dosing cycle = 2 Weeks**
Thyroid Function Testing	X		X See Note	.	Screening labs performed within 7 days of F1D1 visit do not need to be repeated unless clinically indicated. TSH (reflex to free T3 and free T4 if abnormal TSH result)
Review of Concomitant Medications	X	X			Review at every visit
Pregnancy Test		X See note			Serum or urine (for WOCBP only) test to be performed every 4 weeks or more frequently as per local standards for subjects receiving nivolumab 3mg/kg every 2 weeks.
Efficacy Assessments					
Radiographic Tumor Assessment			X		Tumor assessments are conducted every 6 weeks (± 7 days), from first dose for the first year on treatment, then every 12 weeks after the first year on treatment, until documented disease progression (Or discontinuation of study therapy in subjects receiving BMS-936558 (nivolumab) beyond progression). Assessments should include chest, pelvis, and abdomen (with contrast, unless contraindicated) as well as any area that is being monitored. Follow RECIST 1.1 criteria. Subjects with a history of brain metastasis should have surveillance CT/MRI approximately every 6 weeks, or sooner if clinically indicated. (MRI is preferred)
Patient reported outcomes (PRO) Assessment	X			X**	**For F1D1**: performed PRIOR to first dose of nivolumab (day -3 to +1). **For on study visits**: EQ-5D will be performed PRIOR to any study procedures and treatment. **Assessment will be performed on Day 1 of every 6th cycle (every 12 weeks) for the first 12 months, then every 6 months thereafter for the on Day1 remainder of the treatment period, as permitted by local

Table 5.1-6: On-Study Assessments (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase

Procedure	F1D1	Each cycle on Day 1 (± 3 days)	Every 3 cycles on Day 1 (± 3 days)	Every 6 cycles on Day 1 (± 3 days)	Notes 3mg/kg dosing cycle = 2 Weeks
					law.
Health Resource Utilization		X			Except cycle 1. To include: concomitant medication collection.
Clinical Drug Supplies					
BMS-936558- nivolumab *	X	X			First dose must be administered within 3 business days of enrollment in Nivolumab Crossover Extension Phase Record Study Drug Infusion start and stop times. * Subjects may be dosed no less than 12 days from previous dose

Table 5.1-7:	**Follow-up and Survival Procedures (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase**		
Procedure	**Initial Follow-Up Phase** **(100 days from date of last study treatment)** **Follow-up Visits 1 (XX01) and 2 (XX02)** XX01 to occur approximately 35 days (±7 days) after last dose or coinciding with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after last dose XX02 to occur approximately 80 days (±7 days) after XX01.	**Further Follow-up Phase** **(beyond XX02)**	**Notes**
Radiographic Tumor Assessment	X*	X	For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed according to the on-study assessment schedule until PD, withdrawal of consent, death, lost to follow-up, *Radiographic assessments for subjects who have not experienced PD ***must*** be obtained according to the on-study assessment schedule, and ***not*** delayed until XX01 or XX02.
Patient reported outcomes Assessment (PRO)	X	X	EQ-5D only Beyond 100 days from the last dose of study therapy, the EQ-5D will be administered every 6 months thereafter, as permitted by local law.
Safety Assessments			
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	X	X*	*Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent,

Table 5.1-7:	**Follow-up and Survival Procedures (CA209078) For Subjects Previously Randomized to Docetaxel Entering Nivolumab Crossover Extension Phase**		
Procedure	**Initial Follow-Up Phase** **(100 days from date of last study treatment)** **Follow-up Visits 1 (XX01) and 2 (XX02)** XX01 to occur approximately 35 days (±7 days) after last dose or coinciding with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after last dose XX02 to occur approximately 80 days (±7 days) after XX01.	**Further Follow-up Phase** **(beyond XX02)**	**Notes**
Laboratory Tests	X		CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride), AST, ALT, total bilirubin, alkaline phosphatase, glucose, LDH, TSH (reflex to free T3 and free T4 if abnormal result) Note: Repeat at Visit 2 only of study drug toxicity persists
Pregnancy Testing	X		
Review of Concomitant Medications	X		
Collection of Survival Information	X	X	Every 3 months (±14 days) until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit to update survival information and assess subsequent anti-cancer therapy.

5.1.1 Retesting During Screening

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

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments are included in Table 5.1-1 and Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- Nivolumab Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system (randomization)
- Serious Adverse Event (or eSAE) case report forms
- Pregnancy Surveillance Forms
- RECIST 1.1 Pocket guide
- Lung Cancer Symptom Score and EuroQol Group's EQ-5D questionnaires.

5.3 Safety Assessments

Screening Assessments

Screening assessments and procedures must be completed within 28 days prior to randomization, in accordance with Table 5.1-1.

- A complete medical history and concomitant medications, including review of prior systemic treatment received for NSCLC
- Assessment of pre-treatment signs and symptoms
- Patient reported outcomes Assessments (PRO): Lung Cancer Symptom Scale (LCSS) and EuroQol Group's EQ-5D
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 3 calendar days prior to first dose.
- Physical examination and physical measurements including height, and weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status (see Appendix 1).

- Laboratory tests include:
  - Blood for complete blood count (CBC) with differential, including neutrophil and lymphocyte count
  - Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, amylase, lipase and LDH)
  - AST, ALT, total bilirubin, alkaline phosphatase, albumin
  - TSH, free T3 and free T4
  - Hepatitis B virus surface antigen (HBV sAg) and Hepatitis C virus antibody (HCV Ab)
  - HIV testing, if applicable
- A pregnancy test for WOCBP will be collected within 24 hours prior to first dose.

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

Amendment 05 Update: No retesting for HBV, HCV, or HIV is required during the Nivolumab Crossover Extension Phase. For subjects moving in to the Nivolumab Crossover Extension Phase, please refer to Table 5.1-5 for the schedule of screening assessments.

On-Study Safety Assessments and Procedures

The following assessments will be monitored according to the frequency for each treatment Arm starting on Cycle 1 Day 1 and will continue at the specified frequency until discontinuation from the study. (See Table 5.1-2 and Table 5.1-3 for frequency of testing by treatment arm).

- Patient reported outcomes Assessments (PRO): Lung Symptom Cancer Scale (LCSS) and EuroQol Group's EQ-5D. (For subjects treated in the Nivolumab Crossover Extension Phase, ONLY the EQ-5D assessment will be completed according to Table 5.1-6. The LCSS will not be completed in the Nivolumab Crossover Extension Phase.)
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest should be obtained within 3 calendar days prior to each dosing and at any time the subject has any new or worsening respiratory symptoms. (Also monitor amount of supplemental oxygen if applicable). If a subject shows changes in oxygen saturation or supplemental oxygen requirement, or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm contained within the Investigator's Brochure.
- AEs and SAEs continuously throughout the study
- Physical examination and physical measurements including weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status (see Appendix 1)
- Laboratory tests within 3 calendar days prior to the dosing, to include:
  - CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, platelet, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, LDH, amylase and lipase
  - Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin
  - Thyroid function testing includes TSH (reflex to free T3 and free T4 if abnormal result)

- A pregnancy test for WOCBP will be performed every 4 weeks on study regardless of dosing schedule.

Concomitant medications taken throughout the study duration should be recorded within the eCRF.

Blood samples will also be collected for pharmacokinetics and immunogenicity as noted in Table 5.5-1 (for subjects randomized to the nivolumab treatment Arm A only), and for SNP testing as noted in Table 5.1-2 or Table 5.1-3. (For subjects treated in the Nivolumab Crossover Extension phase, NO pharmacokinetics and immunogenicity samples will be collected in the extension phase.)

Additionally, serum samples (for soluble factors and miRNA analyses) will be obtained from all randomized subjects prior to first dose of study drug and every 6 weeks during the treatment period as shown on Table 5.1-2 or Table 5.1-3. (For subjects treated in the Nivolumab Crossover Extension phase, NO serum samples will be collected in the extension phase.)

For subjects who discontinue study treatment due to toxicity, please follow the procedures for the last scheduled visit on study treatment (prior to discontinuation of study therapy and follow-up visits) from either Table 5.1-2 or Table 5.1-3 (and Table 5.5-1 Pharmacokinetic and Immunogenicity Sample Collection Nivolumab Arm).

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.

Amendment 05 Update: Laboratory tests of amylase and lipase are not required for subjects who enroll in the Nivolumab Crossover Extension Phase.

For subjects ernolled in the Nivolumab Crossover Extension Phase, please refer to Table 5.1-6 for the complete schedule of required assessments.

Follow-up and Survival Procedures

Subjects will be monitored for safety according to Table 5.1-4. Subjects will have two follow-up visits for safety. Safety assessments will include: review of concomitant medications, laboratory measurements (CBC, serum chemistry, liver function and thyroid function), and assessment of AEs and SAEs.

Beyond 100 days from the last dose of study treatment, subjects will be followed for ongoing drug related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of consent, or start of subsequent anti-cancer therapy.

Both the LCSS and EQ-5D will be given in FU Visits 1 & 2. In Survival Visits, the EQ-5D will be collected every 3 months for the first year of the Survival Phase, then every 6 months thereafter

Beyond the second follow-up visit, subjects should be followed for survival assessment every 3 months until death, lost to follow-up, or withdrawal of consent. The survival assessments may be performed by phone contact or an office visit.

Amendment 05 Update: For subjects treated in the Nivolumab Crossover Extension phase of the study, please refer to Table 5.1-7 for the complete schedule of required Follow-up and Survival phase assessments.

5.3.1 Imaging Assessment for the Study

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.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

This study has primary endpoint of OS (see Section 8.3 for definition of OS). Every effort will be made to collect survival data on all subjects including subjects who progressed and discontinue study treatment, withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. Survival will be followed either by direct contact (office visits) or via telephone contact, according to Table 5.1-4 until death, withdrawal of study consent, or lost to follow-up.

If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.4.2 Secondary Efficacy Assessments

For secondary efficacy analyses (ORR, PFS, and clinical efficacy in terms of OS, ORR, and PFS in different subgroups, including squamous and non-squamous NSCLC subgroups, PD-L1 positive and PD-L1 negative protein expression subgroups, and Chinese and non-Chinese subgroups), subjects will be monitored by radiographic assessment using RECIST 1.1.[93] High resolution CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice.

Screening assessments should be performed within 28 days of randomization (as shown in Table 5.1-1) and include chest, abdomen, and pelvis, brain (to rule out brain metastasis) and all known or suspected sites of disease. Subsequent assessments (for frequency, refer to Table 5.1-2 or Table 5.1-3) should include chest, abdomen, pelvis and all known or suspected sites of disease using the same imaging method and technique. Subjects with a history of brain metastasis should have surveillance MRI approximately every 6 weeks from first scan or sooner if clinically indicated.

If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound is not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response (CR) is identified in target disease or when progression in bone is suspected.

First radiographic tumor assessment will be conducted at Week 6 (± 7 days) from randomization date and then every 6 weeks from Week 6 (± 7 days) up to first 12 months, then every 12 weeks (± 14 days) until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent or death. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 2 for details of RECIST 1.1).[88]

Subjects achieving a timepoint response of CR or PR will require confirmation of BOR determination as per RECIST 1.1 at their next scheduled tumor assessment in the first year and at least 4 weeks apart in the second half of the year. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (± 7 days).

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5.8.3 Healthcare Resource Utilization

Healthcare resource utilization data associated with hospitalizations and non-protocol specified medical visits related to either study therapy or disease will be collected for all randomized subjects. The healthcare resource utilization will be assessed during the study according to treatment arm assignments below:

- Treatment arm A (nivolumab): Day 1 of each cycle (every 2 weeks) except Cycle 1 and at the first 2 follow-up visits after discontinuation of study treatment.
- Treatment arm B (docetaxel): Day 1 of each cycle (every 3 weeks) except Cycle 1 and at the first 2 follow-up visits after discontinuation of study treatment.

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug 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 drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, 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 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, 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 (eg, 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)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject'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 within 100 days of discontinuation of dosing. Subjects, who are randomized and never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. 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 subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug 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).

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject 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).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study drug exposure, including during at least 5 half lives after product administration. 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 Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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 BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 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 6.1.1 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.

6.7 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.

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see the Evaluation and Management Guidelines found in the Investigator Brochure.[22]

6.7.1 Adverse Events of Interest

Definition of Immune-mediated Adverse Events

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

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. IMAEs are limited to subjects who 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.

Table 6.7.1-1 below provides a summary of the IMAEs category and their respective PTs.

Table 6.7.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A DMC will be established to provide oversight of safety and efficacy considerations in protocol CA209078, and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. Efficacy will also be reviewed by the DMC - as part of the benefit-to-risk assessment and for the formal analyses of TTF and OS.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership team will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes in study conduct are required.

After meeting, the DMC will notify the clinical study leadership group that it has met and will provide recommendations about the study by telephone or email. Detailed procedures to deliver and address the DMC recommendations are described in the BMS Standard Operating Procedure, which specifies the establishment and operation of clinical trial DMCs. Any recommendation by the DMC regarding study modification will be submitted to the clinical study leadership team within pre-specified business days of the DMC meeting.

The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Details of DMC responsibilities and procedures will be specified in the DMC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size is calculated in order to compare the overall survival (OS) between subjects randomized to receive nivolumab and subjects randomized to receive docetaxel. Approximately 500 subjects will be randomized (Intent-To-Treat (ITT) population) to the nivolumab and docetaxel arms in a 2:1 ratio. At least 382 deaths will be required for the final analysis of OS. A formal OS interim analysis will be conducted when at least 291 deaths (76% information fraction) have been observed.

Simulations were run in R to calculate the power of the (weighted) log-rank test.

A mixed population was generated as follows: 500 subjects were randomly assigned to 3 cohorts with 40% squamous (SQ) subjects, 30% non-squamous (NSQ) PD-L1 positive subjects and 30% non-squamous (NSQ) PD-L1 negative subjects.

Heterogeneity of treatment effects among histology and PD-L1 status subgroups was considered for the calculation of overall power and number of events at interim and final analyses of OS.

1. For docetaxel, median Overall Survival (mOS) is assumed to be 10 months for SQ and 12 months for NSQ, as per Asian data.[94,95,96,97,98,99] Exponential distributions of OS times are assumed.
2. For SQ subjects from nivolumab arm, a hazard ratio of 0.6 (mOS nivolumab vs docetaxel: 16.7 vs 10 months) and exponential distribution of OS times are assumed. Assumption on treatment effect is based on results from the Phase 3 Study CA209017 (HR: 0.59; 95% CI: 0.44 - 0.79).
3. For NSQ subjects from nivolumab arm, non proportional hazard models are assumed based on results from the Phase 3 study CA209057. Piecewise exponential models are used to model survival function. For the NSQ PD-L1 positive subjects, a 4-month delay effect (exponential distribution with mOS of 12 months) followed by an exponential distribution with mOS of 24 months was used in the model, providing an overall mOS of 20 months. For the NSQ PD-L1 negative subjects, the piecewise exponential model was as followed: for the first 2 months, survival function is assumed to follow an exponential distribution with mOS of 5 months; after Month 2, an exponential distribution with mOS of OS 18 months, providing an overall mOS of 12.8 months.

Overall survival (OS) in all comers was compared between nivolumab and docetaxel, using a two-sided log-rank test with a significance level of 5%. Fleming-Harrington (FH) weighted log-rank test was also used as it is known to be more efficient for testing survival difference when a delay effect is present. The power of both the log-rank and FH weighted log-rank tests, using G (rho = 0, gamma = 1) weights in the terminology of Fleming and Harrington was assessed. To control the overall Type I error rate under a two-sided 5%, significance levels of 0.020 and 0.044 were used at the interim and final analyses to decide if the study could be stopped for efficacy. These significance levels were calculated using the Lan-DeMets error spending function by East (version 6). Hazard ratios (HR) were estimated using Cox proportional hazards model with treatment arm as the only covariate in the model.

At both IA OS and FA OS, a consistency check will be performed first followed by superiority test (hierarchical testing). Consistency was defined if the observed HR for OS maintains at least 50% of the risk reduction of death in the global studies. The probability that the observe HR is not greater than the consistency HR threshold was calculated at both the interim and final analyses i.e. the probability that the simulated HR ≤ the consistency HR among all simulated trials.

The impact of crossover effect was assessed. Power and hazard ratios were calculated assuming 0%, 5%, 10%, 15% and 20% crossover rates in the control arm. For subjects in the control arm who were identified as crossover, their survival time were simulated based on the OS distribution of the treatment arm according to their histology and PD-L1 status.

All results were generated by 5000 simulations. Accrual information used in the simulations had the same pattern as the actual data at time of the protocol amendment (500 subjects were accrued in 11 months). Simulation results are displayed in Table 8.1-1.

In absence of cross over, IA OS (291 deaths) and FA OS (382 deaths) occurred approximately at 24 months (13 months of minimum follow-up) and 37 months (26 months of minimum

follow-up) respectively. Using the log-rank test, cumulative power was 73% and 96% and average HR was 0.70 and 0.67 at the interim and final analyses, respectively. Power reached 86% and 98% accordingly with the weighted log-rank test. Probability of Technical Success (PTS) for consistency check at the interim analysis was 95% (ie. the probability that the observed HR ≤ 0.850). At the final analysis, probability of technical success for consistency check was 98% (ie, probability that the observed HR ≤ 0.835 was 98%). PTS of the log-rank test decreases when cross-over is present. PTS of the weighted log-rank test decreases as well but less than the conventional log-rank test. PTS for consistency check remains above 90% for crossover rates up to 20%.

Table 8.1-1: Simulations Results

	No Crossover	5% Crossover	10% Crossover	15% Crossover	20% Crossover
Events at IA/FA	291/382	291/382	291/382	291/382	291/382
Timing for IA/FA (months)	24/37	24/38	24/38	24/38	24/38
Expected HRs at IA/FA	0.70/0.67	0.71/0.69	0.73/0.71	0.74/0.72	0.75/0.73
Consistency HR thresholds at IA/FA (maintaining 50% of risk reduction)	0.850/0.835	0.855/0.845	0.865/0.855	0.870/0.860	0.875/0.865
PTS for log-rank test at IA/FA	73%/96%	69%/94%	63%/90%	59%/86%	53%/82%
PTS for weighted log-rank test at IA/FA	86%/98%	82%/97%	77%/94%	72%/91%	67%/88%
PTS for consistency check	95%/98%	93%/98%	93%/97%	91%/96%	90%/94%

After the first ~380 randomized subjects have been followed for at least 8 months (approx. 16 months after study initiation), TTF is to be compared across treatment groups using a weighted log-rank test.[100,101] With one-sided type 1 error of 0.025, the power for the weighted log-rank test of TTF was ~95% per simulations using data observed in global pivotal studies (CheckMate 057 and 017), and, adjusted for the proportion of SQ and NSQ in this study. Expected HR for TTF was 0.7.

8.2 Populations for Analyses

- Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS
- Randomized subjects: All enrolled subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of efficacy and baseline characteristics
- TTF population: All randomized subjects with at least 8 months of follow-up at the time of TTF analysis. This dataset will be used for all ITT analyses at the TTF interim analysis. Subject's follow-up time is defined here as the time between randomization date and

database cutoff date regardless of subject disposition (ie, intent-to-treat population). The clinical database cutoff date will occur when the first approximately 380 randomized subjects will have at least 8-month of follow-up.

- Treated subjects: All randomized subjects who received at least one dose of nivolumab or docetaxel. This is the primary dataset for analyses of dosing and safety
- Treated subjects among TTF population: This is the primary dataset safety and exposure analyses on the treated subjects among TTF population
- PK subjects: All subjects treated with Nivolumab who had available serum time-concentration data
- Immunogenicity subjects: All subjects treated with Nivolumab who had available ADA data
- Biomarker subjects: All randomized subjects who had available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

- Consistency in OS benefit is defined as maintaining 50% of the risk reduction of death from CheckMate 057 and CheckMate 017 after adjusting for the patient distribution and the use of anti-PD-1/PD-L1 agents in the docetaxel arm.
- The primary endpoint of this study is OS. It is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive.

OS will be followed continuously while subjects are on the study treatment and every 3 months via in-person or phone contact after subjects go off the study treatment.

8.3.2 Secondary Endpoint(s)

The secondary efficacy endpoints in this study include ORR, progression free survival (PFS), time to treatment failure (TTF) and disease-related symptom deterioration by Week 12/ Week 24 as measured by LCSS. Detailed definitions of these endpoints are described below:

8.3.2.1 Objective Response Rate

The ORR is defined as the number of subjects whose BOR of CR or partial response (PR) divided by the number of randomized subjects. BOR is defined as the best response designation, as determined by the investigators, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anticancer therapy (excluding on-treatment palliative radiotherapy of CNS, skin or bone non-target lesions), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue nivolumab beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression. Tumor assessments will be assessed every 6 weeks from the first on-study radiographic assessment (at Week 6) until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent or death.

8.3.2.2 Progression Free Survival

PFS is defined as the time from randomization to the date of the first documented tumor progression as determined by investigators per RECIST 1.1, or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not have disease progression or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions, skin lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy.

8.3.2.3 Time to Treatment Failure

Time to Treatment Failure (TTF) is defined as the minimum of the time from randomization to the following dates:

- disease progression date (RECIST 1.1 or Clinical)
- death date
- last dose date if subject discontinued from treatment for any reasons other than 'maximum clinical benefit' or 'administrative reasons by sponsor'[102].

TTF is considered as event at the randomization date for subjects who were randomized but not treated. Clinical progression date is considered for time to treatment failure only when treatment is discontinued due to clinical disease progression. For nivolumab subjects treated beyond RECIST 1.1 progression, the event will be at RECIST 1.1 progression date. TTF is censored at the last dose date for subjects who discontinued treatment (without RECIST 1.1 progression) due to maximum clinical benefit or administrative reason by sponsor. TTF is censored at the last dose date for subjects who continued on treatment without progression or death.

TTF will be analyzed at the interim analysis of TTF only

8.3.2.4 Rate of Disease-related Symptom Deterioration

Disease-Related Symptom deterioration Rate by Week 12 and by Week 24 is defined as the proportion of randomized subjects who had 10 points or more increase from baseline in Average Symptom Burden Index (ASBI) score at anytime between randomization and Week 12/Week 24 respectively.

The LCSS is a measure of disease-related symptoms and quality of life suited to use in patients suffering from lung cancer. It includes six items measuring loss of appetite, fatigue, coughing, shortness of breath, hemoptysis, and pain. Three additional items measure overall symptom burden, disease-related functional limitations, and quality of life. The questionnaire uses a 24-hour recall period, and responses for each item are captured using a 100-mm visual analog scale (VAS). Scores for individual items ranging from 0 (no symptomatology or highest quality

of life) to 100 (worst symptomatology or quality of life) are derived by dividing the length of the line drawn from the lowest possible response to the patient's response by the length of the VAS and multiplying the resulting quotient by 100. An average symptom burden index (ASBI) score can be derived as the average of scores for the six symptom-related items with a clinically meaningful change in ASBI score being defined as 10 points. Accordingly, a meaningful deterioration in symptoms as measured by the ASBI is reflected in a mean post-baseline score change ≥ 10 points.[103,104,105]

The LCSS questionnaire is completed on Day 1 of the scheduled cycle for the first 6 months on study treatment, then every 6 weeks Table 5.1-2, Table 5.1-3, and Table 5.1-4 (for Follow-up visits) for frequency of assessments on study for each treatment arm.

8.3.2.5 Rates of Treatment Related Selected AEs and SAEs

The secondary safety endpoint is the rate of treatment related selected AEs and SAEs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Methods of Primary Endpoint

OS is the primary endpoint of this study.

At both the interim OS analysis and final OS analysis, a 2-step hierarchical testing will be performed. First, a check for consistency with global data in HR for OS will be performed. This is to mitigate loss of power due to confounding effects of cross-over (subjects receiving anti PD-1/PD-L1 agents in the comparator arm).

If consistency in OS with global data is demonstrated, superiority for OS will be tested. The distribution of OS in two randomized arms will be compared at the interim and final analyses via a two-sided α (adjusted for the interim) weighted, log-rank test stratified by the stratification factors used for randomization as determined per IVRS, ie, histology (squamous vs non-squamous)/ PD-L1 Status (positive vs negative/unevaluable)/ ECOG Performance status (0 vs 1). The weighted log-rank test will use G (rho = 0, gamma = 1) weights, in the terminology of Fleming and Harrington[100,101]

The unweighted hazard ratio (HR) and the corresponding 100x (1- alpha)% confidence interval (CI) (adjusted for the interim) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate with the same stratification factors mentioned above. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method, based on a log-log transformed CI for the survivor function S(t).[106,107] Survival rates at 6, 12, and 18 months will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood formula.

[redacted]

[redacted]

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. 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.

Frequency, management and resolution of IMAEs will be analyzed. A tabular summary and comparative analysis between treatment arms of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-toonset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE are individually characterized:

- pneumonitis IMAEs
- diarrhea/colitis IMAEs
- hepatitis IMAEs
- nephritis and renal dysfunction IMAEs
- rash IMAEs
- endocrine IMAEs by subcategories including adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes

8.4.4 Pharmacokinetic Analyses

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

[redacted]

[redacted]

8.5 Interim Analyses

One interim analysis of OS is planned after 291 OS events have been observed (76% of the total number of OS events at the final analysis). This formal comparison of OS will allow for early stopping for superiority. Lan-DeMets α spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of OS events at the time of the interim analysis. However, if the analysis were performed exactly at 291 OS events, the boundary for declaring superiority would be p-value < 0.020. The boundary for declaring superiority for the final analysis after 382 OS events would be p-value < 0.044. An independent statistician external to BMS will perform the analysis. In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

A Time to Treatment Failure (TTF) interim analysis is planned after the first ~380 randomized subjects have been followed for at least 8 months (projected to occur approx. 16 months after study initiation). The DMC will review the safety and efficacy data from the TTF interim analysis. There is no alpha spending nor penalty for TTF analysis: this interim analysis is considered as a bridging strategy. If TTF is statistically significant at 1-sided 0.025 level, safety and ORR will be described (no formal comparison) using the TTF population. Regardless of whether TTF is positive or negative, study will continue to the planned OS interim/final analysis.

At the TTF analysis, the distribution of TTF will be compared in the two randomized arms via a 1-sided, unstratified weighted log-rank test. The one-sided weighted log-rank p-value will be reported using G (rho = 0, gamma = 1) weights, in the terminology of Harrington and Fleming.[103,111] The FH method (with rho = 0 and gamma = 1) leads to a loss of power when treatment effect is not delayed but has higher power when a delay of more than 2 months is observed, which is expected for TTF, based on data from global studies CheckMate 017 and 057. TTF will also be compared using a regular log rank test.

The hazard ratio (HR) and the corresponding 1-sided 97.5% CI upper bound will be estimated in an unstratified Cox proportional hazards model using randomized arm as a single covariate. The TTF curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median TTF will be constructed based on a log-log transformed CI for the survivor function S(t).

As sensitivity analysis, TTF will be analyzed using the primary definition but censoring TTF for discontinuation due to due to patient preference (subject withdrew consent, subject lost to follow up) or physician withdrawal (subject no longer meets study criteria, administrative reason by sponsor).

At the TTF analysis, ORR will be analyzed descriptively using the TTF population. In addition, analyses will be repeated using the Chinese subjects among the TTF population, and efficacy

will also be assessed by histology. BOR will be summarized by response category and treatment group and ORR will be computed with the exact 95% CI using Clopper-Pearson method. TTR and DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) of the TTF population. Study conduct and study population will be summarized on the TTF population. Exposure and safety (including death summary) will be summarized on the treated subjects among TTF population.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (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).

9.1.2 Monitoring

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 BMS 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 BMS.

9.1.2.1 Source Documentation

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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator 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, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and

the following non-investigational product(s) Dexamethasone. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject 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.

Note: For study drug sourced by site, and not supplied by BMS or its vendors, 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.

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

9.2.3 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 BMS 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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, including any paper or electronic 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 .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 BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 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 considering the following criteria:

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

The data collected during this study are confidential and proprietary to BMS. 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 BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AEOSIs	Adverse Events of Special Interests
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic lymphoma kinase (CD246)
ALT	Alanine Aminotransferase
APC	Antigen-presenting cells
ASEAN	Association of Southeast Asian Nations
ASR	Age-Standardized Rate
AST	Aspartate Aminotransferase
Bcl- x_L	B-cell lymphoma-extra large
BID	Twice per day
B7-DC	Human B7 –dendritic cell
B7-H1	Human B7 homolog 1
BMS	Bristol-Myers Squibb
BOR	Best overall response
BSC	Best supportive care
BTLA	B-and T-cell attenuator
CD28	Cluster of differentiation 28
CD273	Cluster of differentiation 273
CD274	Cluster of differentiation 274
C57BL/6	C57 black 6 breed mouse
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
CMV	Cytomegalovirus
CNS	Central nervous system
COX2	Cyclooxygenase-2
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T-Lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP	Cytochrome P450
D	Day
DCF	Data clarification form
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee

DOOR	Duration of objective response
ECL	Electrochemilumeminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EI	Equivalence interval
ELISA	Enzyme-Linked Immunosorbent Assay Test
EOI	End-of-infusion
ESOI	Events of special interest
EU	European Union
FFPE	Formalin Fixed, Paraffin-Embedded
FLIP	caspase-8 (FLICE)-like inhibitory protein
FSH	Follicle stimulating hormone
FU	Follow up
GCP	Good clinical practices
GMP	Good manufacturing practices
HBV sAg	Hepatitis B virus surface antigen
HCV Ab	Hepatitis C virus antibody
HCG	Human Chorionic Gonadotropin
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HTA	Health authority
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICOS	Inducible T-cell co-stimulator (CD278)
IDO	Inducible co-stimulator
IFN	Interferon
IFNGR1	Interferon Gamma-receptor-1
IFN-γ	Interferon Gamma
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medical product
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IRB/IEC	Institutional review board/independent ethics committee
IV	Intravenous

IVRS	Interactive voice response system
KM	Kaplan-Meier curve
LCCS	Lung Cancer Symptom Scale
LFT	Liver function test
LMP	Low-molecular-mass protein
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
mg	Milligram
mL	Milliliter
MLR	Mixed Lymphocyte Reaction
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
M^2	Square meter
NCI	National Cancer Institute
NIMP	Non-investigational medical product
NK	Natural killer
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NOS	Not otherwise specified
NOS2	Nitric oxide synthase 2
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PGE2	Prostaglandin E2
PK	Pharmacokinetics
PO	By mouth
P19	Serine-protease inhibitor
PPK	Population pharmacokinetic
PR	Partial response
PRO	Subject reported outcomes
PSA	Prostate-specific antigen
PVG	Pharmacovigilance
q	Every
PRO	Patient reported outcomes

RAG	Recombination activating gene
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOC	System/Organ/Class
SOP	Standard operating procedures
Src	Sarcoma
STAT	Signal Transducers and Activators of Transcription
TAP1	Transporter associate with antigen processing 1
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIL	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRAIL	Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Treatment
Tregs	Regulatory T cells
TTF	Time To Treatment failure
TTR	Time to objective response
ULN	Upper limit of normal
Vz	Volume of Distribution
WBC	White blood cell
WOCBP	Women of child bearing potential

APPENDIX 2 RECIST 1.1 GUIDELINES

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, saggital 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 < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, 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 examples in Appendix 2 and 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:

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

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is defined as the best response designation, as determined by the investigators, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anticancer therapy,

whichever occurs first. 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 3.3.2A 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 3.3.2B is to be used.

Table 3.3.2A: 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 3.3.2B: 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.

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: 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 3 MANAGEMENT OF SAFETY ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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.

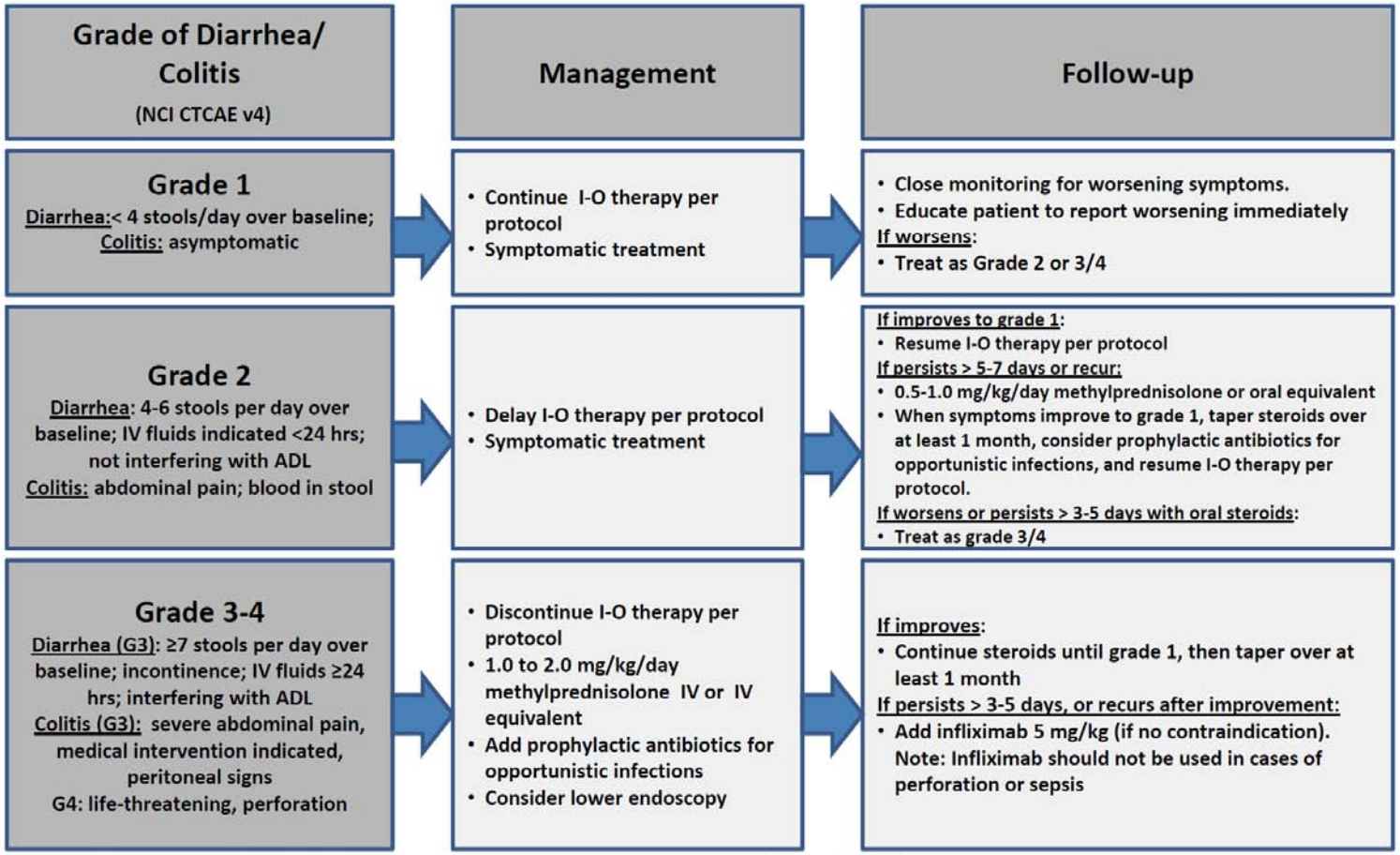
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

Updated 05-Jul-2016

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.

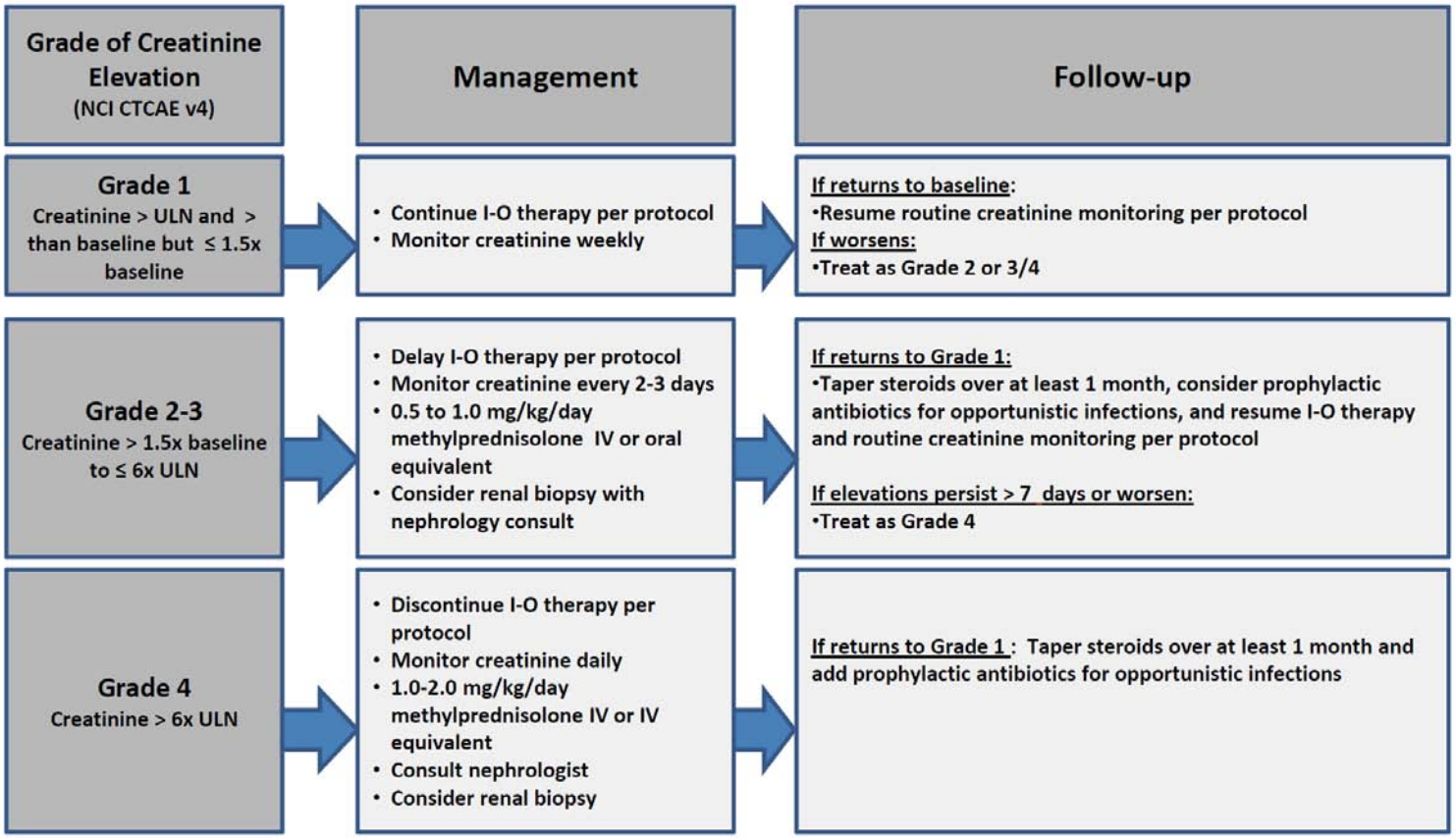


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

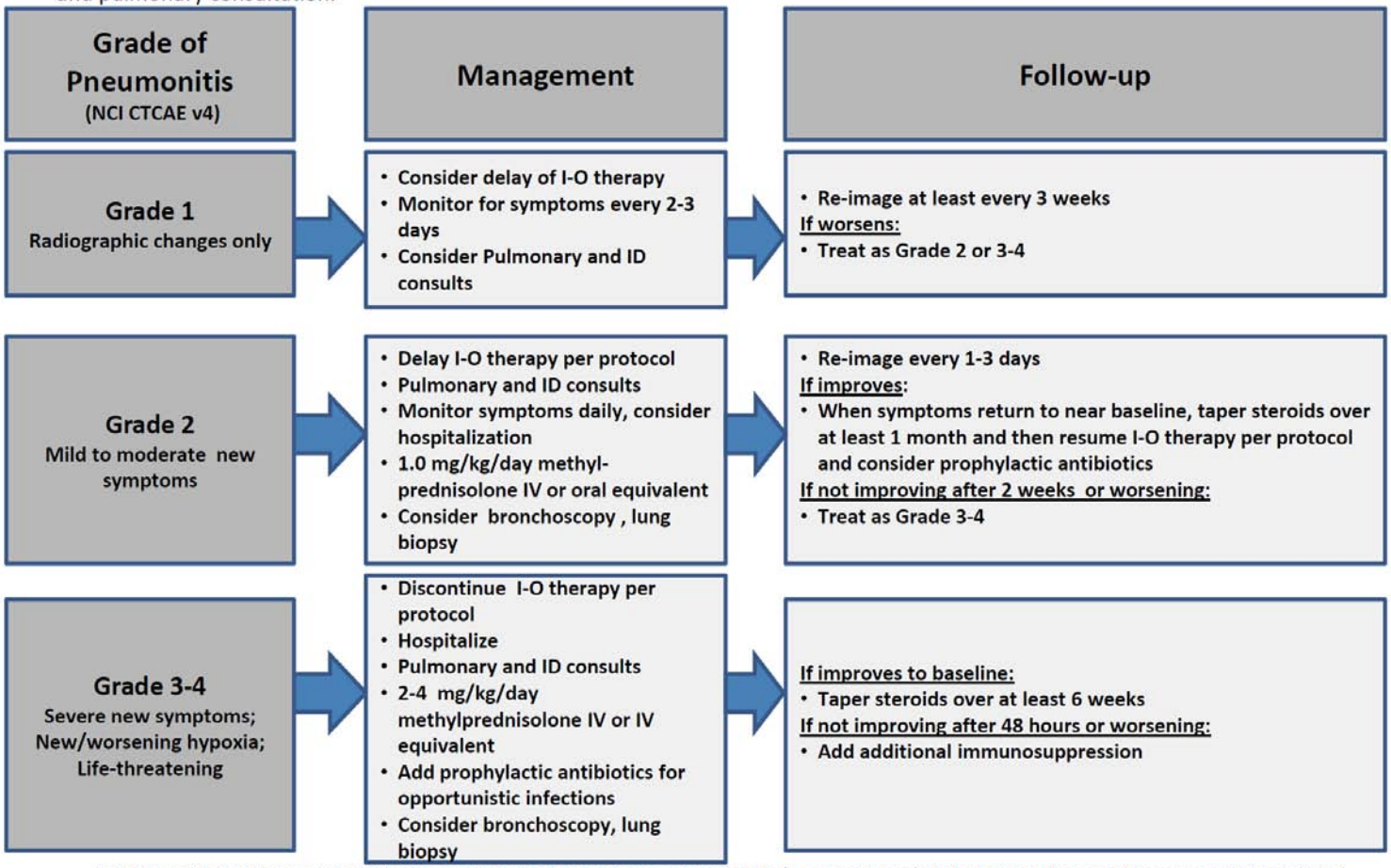


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

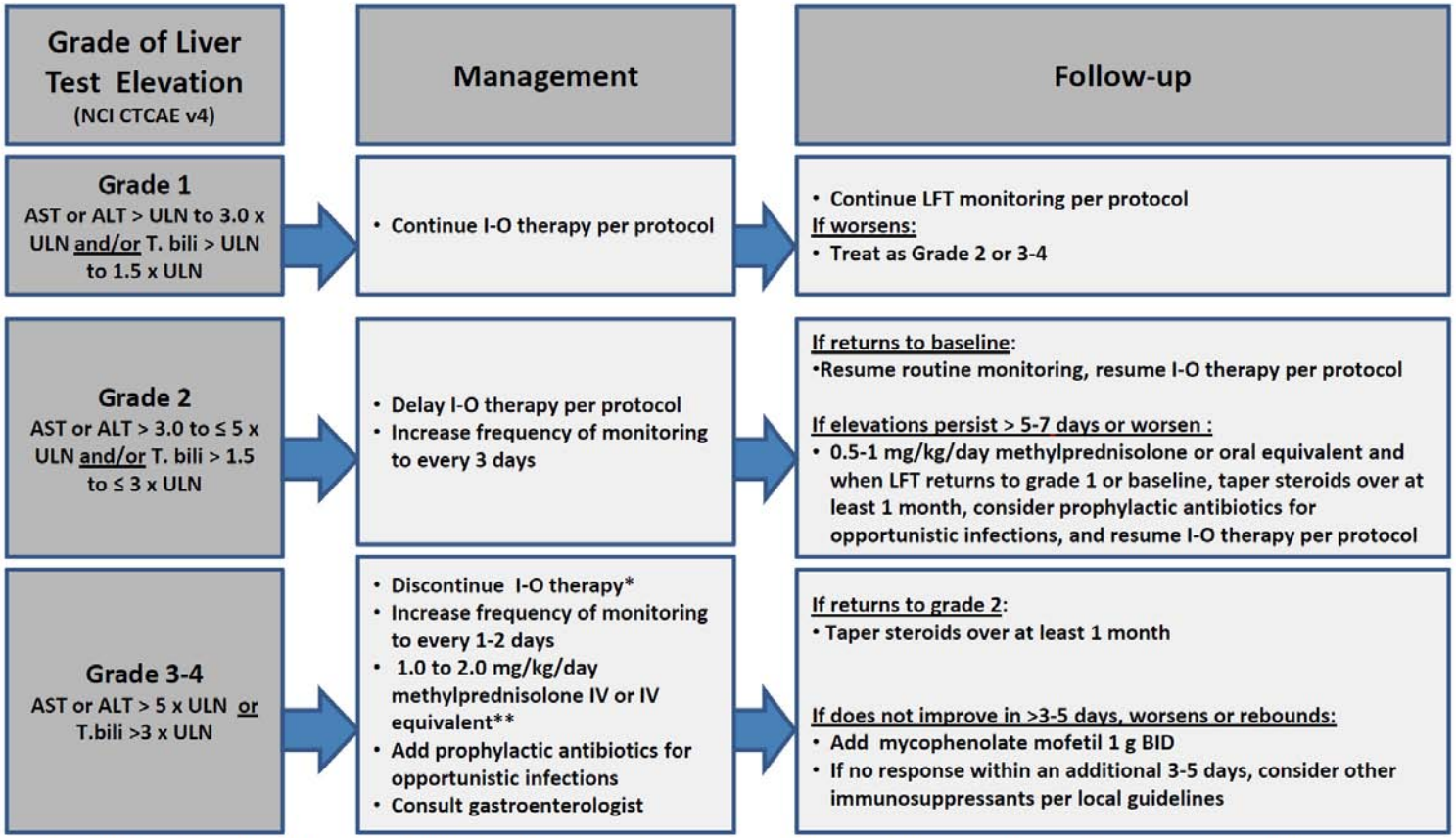


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

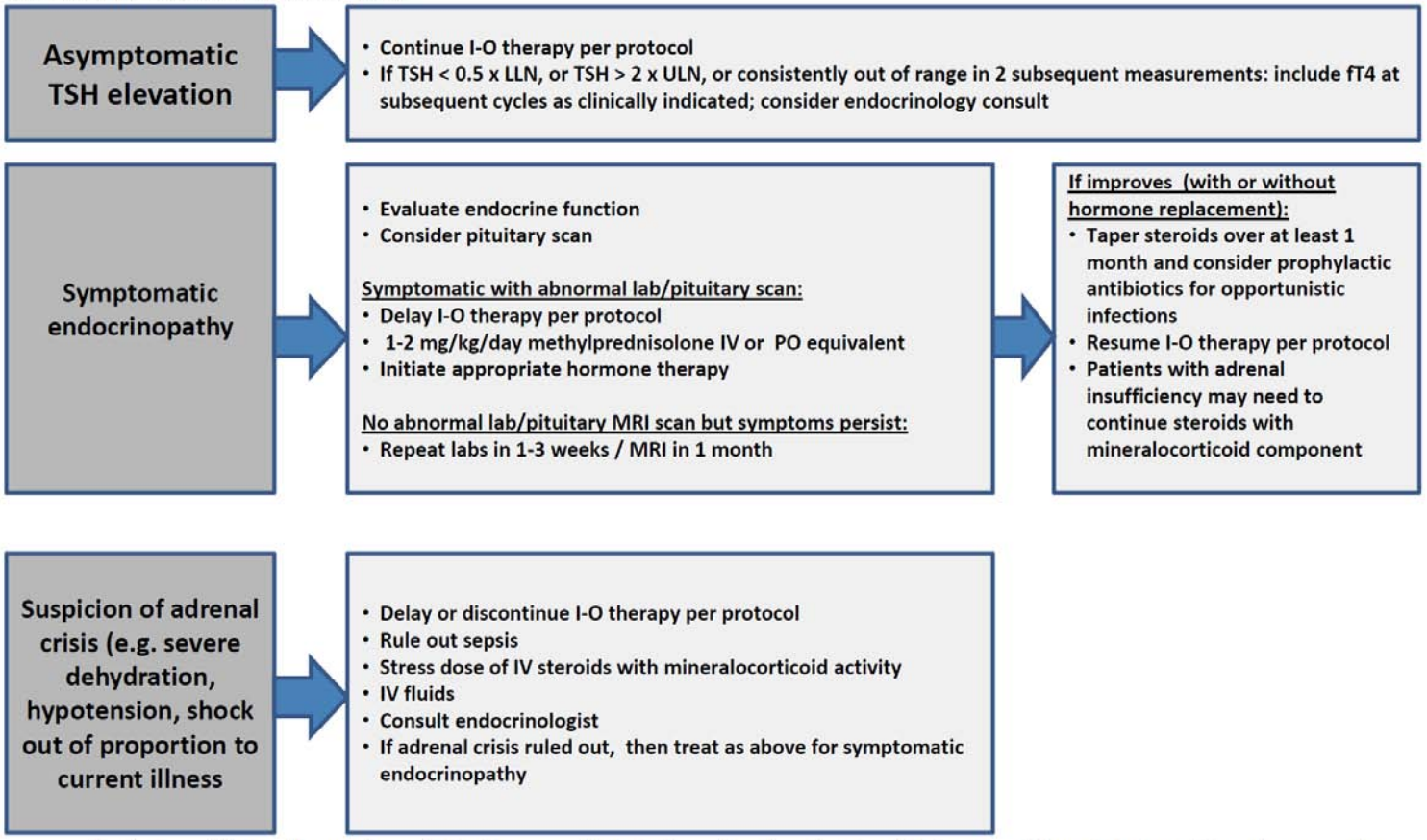
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy 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.

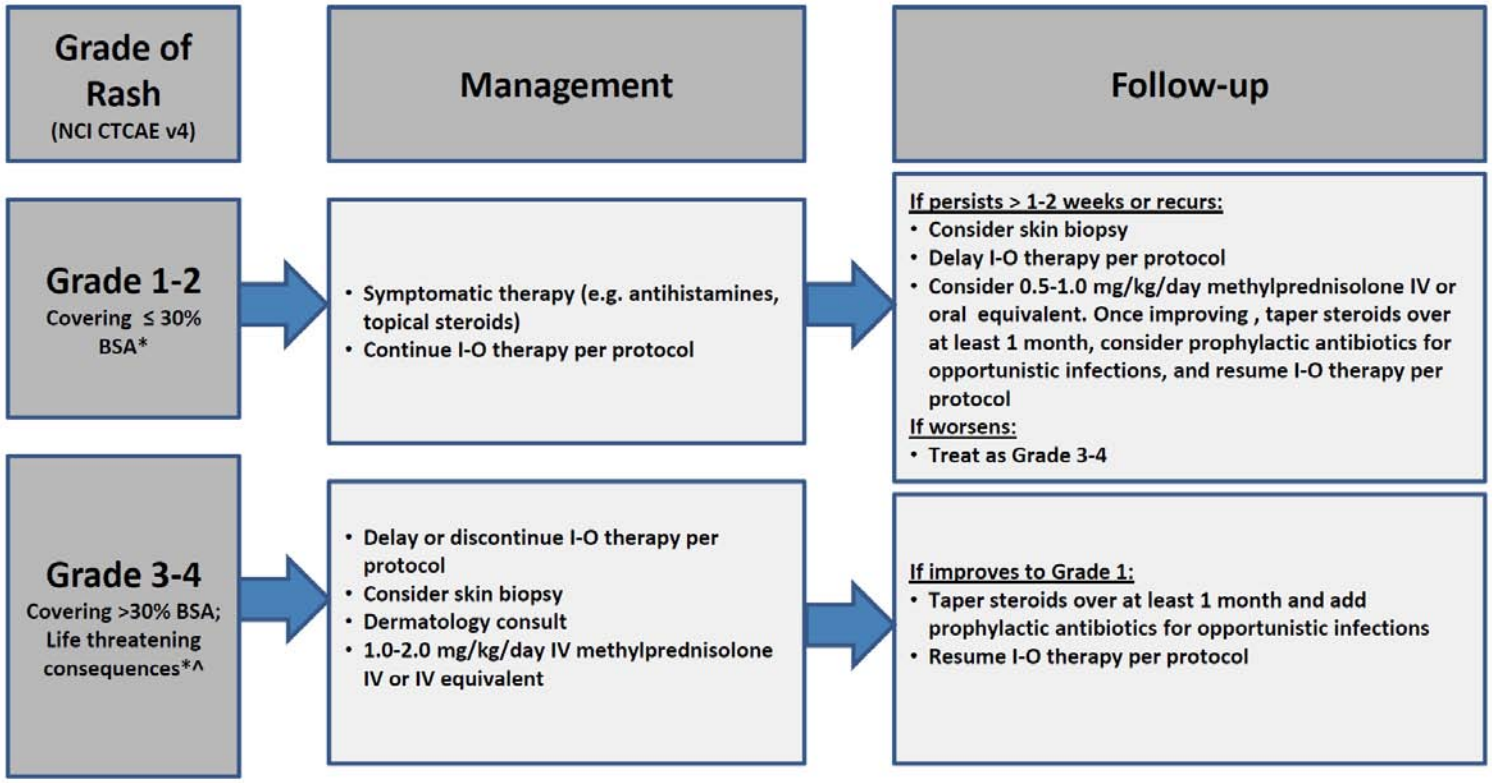


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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.

Updated 05-Jul-2016