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Clinical Protocol CA209331

An Open-label, Randomized, Phase 3 Study of Nivolumab or Chemotherapy in Subjects with Relapsed Small-cell Lung Cancer after Platinum-based First Line Chemotherapy

(CheckMate 331: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 331)

Revised Protocol Number: 03
Incorporates amendment(s) 17 and Administrative Letter 04, 05 and 06

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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.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	20-Mar-2018	Incorporates Amendment 17 and Administrative Letters 04, 05 and 06
Amendment 17	20-Mar-2018	• Updated study personnel • Added additional China cohorts in Arm A and Arm B • Added tumor mutational burden and time to symptom deterioration as exploratory objectives • Updated protocol as per nivolumab program standards
Administrative Letter 06	19-Dec-2017	Change in Medical Monitor contact
Administrative Letter 05	06-Dec-2017	Change in Medical Monitor contact
Administrative Letter 04	29-Jun-2017	Change in Medical Monitor contact
Revised Protocol 02	07-Sep-2016	Incorporates Amendment(s) 15 and Administrative Letter 03
Amendment 15	07-Sep-2016	• Remove the planned interim analysis and to modify the timing of the final analysis as a result from a phase 1/2 study (CheckMate 032) which suggested a treatment delayed effect for immunotherapy in Small Cell Lung Cancer. The amendment will also add a sub-study in China to comply with regulatory requirement in that country • Revise the exploratory objective of Lung Cancer Symptom Scale based on results of Checkmate 017 and Checkmate 057 • Other changes include correction of inconsistencies, alignment with latest Nivolumab standards, and investigator brochure.
Administrative Letter 03	05-Feb-2016	Edited misleading/ambiguous sentence about the contraception method to be used.
Revised Protocol 01	15-Dec-2015	Incorporates Amendment(s) 11 and Administrative Letters 01 & 02
Amendment 11	15-Dec-2015	The main purpose of this amendment is to allow the use of different topotecan formulations (powder for injection and oral capsules). Other changes include modification of the treatment assignment for Arm B to allow for treatment with topotecan or amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC patients), clarification of some inclusion/exclusion criteria, correction of inconsistencies and typographical revisions throughout the protocol. Change of Medical Monitor
Administrative Letter 02	08-Dec-2015	Change of Study Director and Medical Monitor
Administrative Letter 01	14-Jun-2015	Criterion deleted given because not applicable to the approved original protocol

Document	Date of Issue	Summary of Change
Original Protocol	22-Apr-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209331

Protocol Title: An Open-label, Randomized, Phase 3 Study of Nivolumab or Chemotherapy in Subjects with Relapsed Small-cell Lung Cancer after Platinum-based First Line Chemotherapy

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Nivolumab 240 mg (flat dose) on Day 1 of a 14-day cycle as an IV infusion over 30 minutes.
- Topotecan: 1.5 mg/m^2 administered as 30-minute IV infusion or 2.3 mg/ m^2 oral capsule (round dose to nearest 0.25 mg) once daily on Days 1 to 5 of a 21-day cycle.
- Amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC treatment): 40 mg/m^2 administered as 5-minute IV infusion once daily on Days 1 to 3 of a 21-day cycle.

Treatment is continued until disease progression, unacceptable toxicity, or other protocol-defined reasons.

Study Phase: 3

Research Hypothesis: Treatment with nivolumab will increase overall survival (OS) as compared with chemotherapy in subjects with relapsed small-cell lung cancer (SCLC) treated with prior platinum-based, first-line chemotherapy.

Objectives:

Primary Objectives

- To compare the OS of nivolumab versus chemotherapy in subjects with relapsed SCLC after platinum-based, first-line chemotherapy.

Secondary Objectives

- To compare the progression free survival (PFS) of nivolumab versus chemotherapy
- To compare the objective response rate (ORR) of nivolumab versus chemotherapy

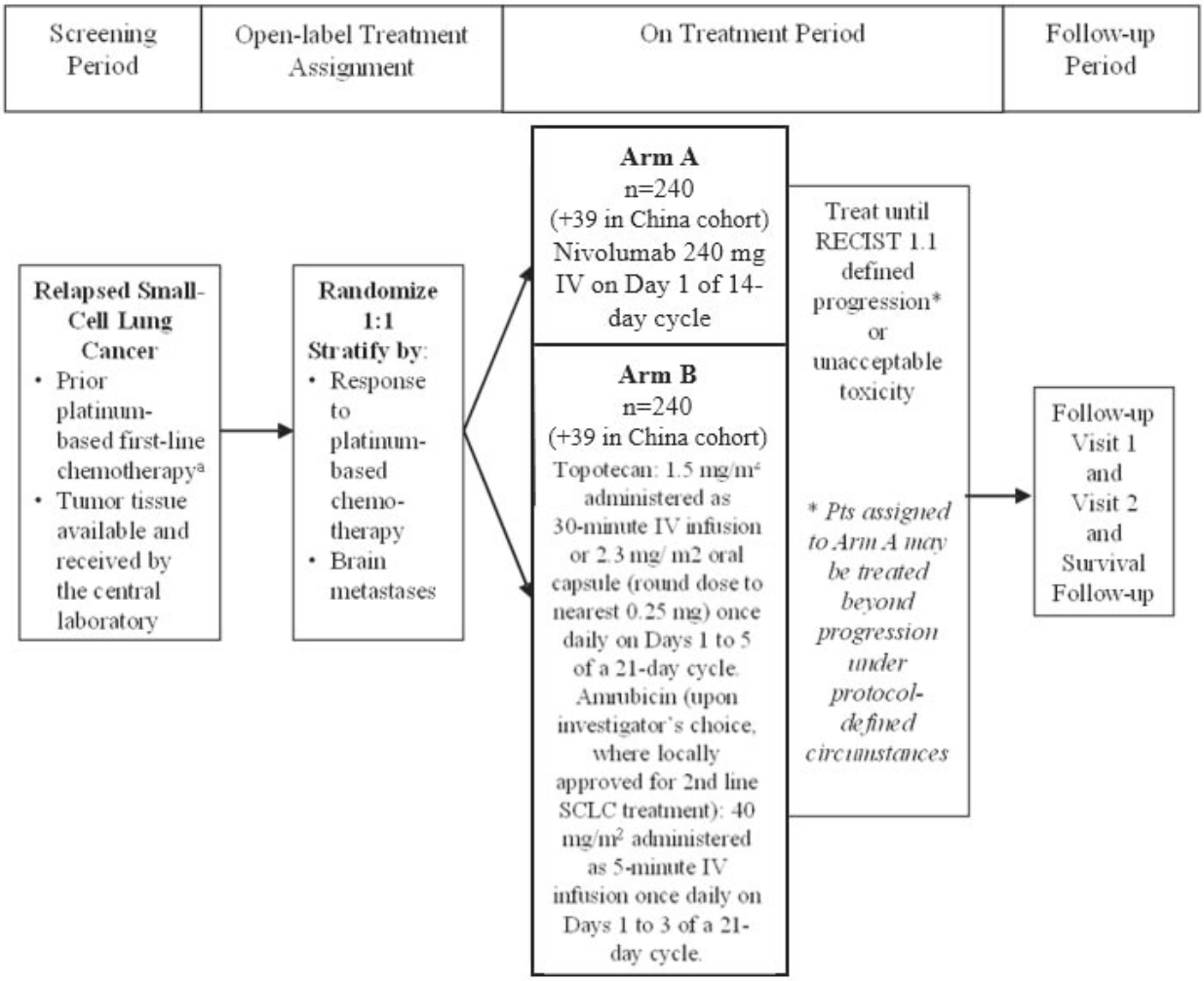
Exploratory Objectives

- To evaluate the safety and tolerability of nivolumab versus chemotherapy
- To characterize pharmacokinetics of nivolumab and explore exposure response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints
- To explore PD-L1 expression as an independent predictive biomarker for OS, ORR, or PFS in nivolumab and chemotherapy groups
- To explore tumor mutational burden expression as an independent predictive biomarker for efficacy in nivolumab and chemotherapy groups
- To correlate potential predictive biomarkers in peripheral blood and tumor specimens, including proteins involved in regulating immune responses (eg, [redacted] PD-L1, [redacted]), mutational as well as

immunohistochemistry (IHC) spectrum, with endpoints such as ORR, PFS and OS in nivolumab and chemotherapy groups

- [redacted]
- To characterize immunogenicity of nivolumab
- To evaluate the proportion of subjects exhibiting disease-related symptom deterioration by 12 weeks and by 24 weeks, as measured by the Lung Cancer Symptom Scale (LCSS) in nivolumab and chemotherapy groups
- To evaluate the time to symptom deterioration (TTSD), as measured by the average symptom burden index (ASBI) of the Lung Cancer Symptom Scale (LCSS), in subjects receiving nivolumab versus chemotherapy
- To assess the subject's overall health status using the EQ-5D Index and visual analog scale in nivolumab and chemotherapy groups.

Study Design: This is a randomized, open-label, two-arm, multicenter, Phase 3 study in adult subjects with relapsed SCLC treated with prior platinum-based, first-line chemotherapy. Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than 4 cycles, they must have had a best overall response (BOR) of a partial or complete response after completion of chemotherapy.



[a] Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than 4 cycles of platinum-based first-line chemotherapy, they must have had a best overall response (BOR) of at least a partial or complete response after completion of chemotherapy.

Study Population:

Key Inclusion Criteria:

Adult men and women with histologically or cytologically confirmed SCLC that recurred or progressed after platinum-based, first-line chemotherapy or chemoradiation therapy. Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy for either limited or extensive stage disease or if less than 4 cycles, must have had a BOR of at least partial or complete response.

Key Exclusion Criteria:

Active symptomatic central nervous system metastases, documented carcinomatous meningitis, active, known or suspected autoimmune disease, and prior treatment 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), topotecan, or amrubicin.

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

Study Drugs for CA209331 - Treatment Phase		
Study Drug	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Topotecan hydrochloride concentrate for solution for infusion	4 mg (1 mg/mL)	IP
Topotecan hydrochloride powder for infusion	4 mg	IP
Topotecan hydrochloride capsules	0.25 mg and 1 mg	IP
Amrubicin hydrochloride powder for solution for injection	50 mg	IP

Study Assessments: OS is the primary endpoint of the study. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subject discontinued the study drugs.

Subjects will be assessed for response by computed tomography (CT) or magnetic resonance imaging (MRI) beginning at 6 weeks (± 5 days) (from the first dose of study treatment) and continuing every 6 weeks (± 5 days) until Week 30 and then every 12 weeks (± 5 days). Tumor assessment will continue until disease progression (or until discontinuation of study drug in patients receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends. All randomized subjects will be evaluated.

Statistical Considerations:

Sample Size: A total of approximately 560 subjects will be randomized at a ratio of 1:1 into two arms: Arm A (nivolumab); Arm B (chemotherapy – ie, topotecan or amrubicin). This includes approximately 78 subjects enrolled in China (~ 16% of the 480 subjects planned to be randomized in global population). If necessary, the China enrollment will continue until the pre-specified sample size of the China sub-population is filled. Additional analyses exploring the consistency of findings in the China sub-population may be conducted. Details of these analyses will be provided in the analysis plan.

The decision to incorporate the China sub-population into the overall population for analysis is the result of a review of the protocol statistical assumptions in comparison to recent data from the CA209032 study in 2L+ SCLC subjects (Hellman MD et al, 2017). The data from CA209032, which were not available at the time of protocol design,

suggest a delayed effect of nivolumab with a non-proportional hazard for survival. Additionally, review of recently generated real-world data for topotecan resulted in updated assumptions for the control arm. Given the updated statistical assumptions, incorporation of the China sub-population into the study analyses grants adequate statistical power by increasing the study sample size.

In this study, the primary endpoint of OS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided). For sample size calculation, non-proportional hazard model with a piecewise exponential distributions in both arms are assumed. Based on published survival curves for topotecan, a 2-piece exponential distribution with an 8-month median OS and taking into account that a limited number of subjects might receive immuno-oncology agents as subsequent therapy in this open-label study, a conservative 5% 2-year survival rate is assumed for the control arm. A delayed effect for nivolumab with a hazard ratio (HR) of 1 for the first 8 months and an HR of 0.5 thereafter is assumed

The final analysis will take place 34 months after FPFV and no formal interim analysis will be conducted. It is anticipated that approximately 480 events will be observed at the time of the analysis, leading to 90% power to detect a difference in overall survival as tested via a log-rank test with a two-sided 0.05 type I error rate. Power calculations were performed using EAST® Software (version 6.4.1).

The secondary endpoints PFS and ORR will be tested hierarchically.

Table 1: Sample Size Justification

Primary Endpoint	**OS**
Power	90%
Alpha level	0.05
Sample size	560
Accrual duration	18 months
Timing of the analysis from randomization of first subject (months)	34
Hypothesized OS rate at 8 months	50% in both arms (HR=1 up to Month 8)
Hypothesized OS rate at 24 months	5% vs 16% (HR=0.5 from Month 8)
Expected Average HR	~0.745
Expected number of event at 34 months	482

Endpoints: 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 subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug. Secondary endpoints include ORR and PFS.

Analyses: All hypothesis testing will be two-sided based on a significance level of 0.05 except for OS. If superiority of OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1) PFS
2) ORR

The formal statistical testing for PFS will take place only if OS is statistically significant and the statistical testing for ORR will take place only if both OS and PFS are statistically significant.

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1 INTRODUCTION AND STUDY RATIONALE

CA209331 is a randomized, open-label, multinational Phase 3 trial of nivolumab (also known as BMS-936558) monotherapy versus chemotherapy in subjects with small cell lung cancer (SCLC) whose disease has relapsed or progressed after prior platinum-based chemotherapy regimen. This study will determine if nivolumab improves overall survival (OS) over chemotherapy in this subject population. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient reported outcomes, and potential predictive biomarkers of nivolumab in subjects with SCLC.

1.1 Study Rationale

1.1.1 Rationale for Investigating Relapsed Small Cell Lung Cancer (SCLC)

SCLC accounts for 15 to 20% of new cases of lung cancer, and nearly 33,900 new cases are expected in the United States (US) in 2012.[1] SCLC is traditionally classified as Limited Stage Disease (LD-SCLC: tumor tissue encompassed within a single radiation port) and Extensive Stage Disease (ED-SCLC: tumor that extends beyond the boundaries of a single radiation port).[2] For LD-SCLC, or Stage IA-IIIB localized disease (T1-4, N0-3, M0), a combined therapeutic approach of radiotherapy, chemotherapy and rarely surgery is used with curative intent.[3] Most patients at diagnosis have ED-SCLC, or Stage IV disease, and are treated with four to six cycles of platinum plus etoposide (PE) which remains the standard chemotherapy regimen for LD- and ED-SCLC.[4] Initial response rate is robust with 70 to 90% response seen in LD-SCLC and 50 to 70% response seen in ED-SCLC.[3] However, overall survival remains poor with median survival for LD-SCLC at 18 to 30 months[5] and for ED-SCLC in the range of 10 to 12 months.[6]

Following platinum-based first-line therapy, about 80% LD-SCLC patients and all of ED SCLC patients have disease progression.[7] Patients whose response after first-line platinum-based therapy last beyond 180 days are the candidates for rechallenge with platinum doublet therapy. Others are treated with single-agent topotecan, the only approved second-line therapy in the US. Approval was based on a Phase 3 study of single agent intravenous topotecan versus a regimen consisting of cyclophosphamide, doxorubicin, and vincristine (CAV) which showed an improved objective response rate (ORR, 24.3% vs 18.3%, P = 0.285) while median survival was similar between two arms (25 weeks vs 24.7 weeks).[8] In another Phase 3 trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed SCLC, the median survival was statistically significantly improved for the topotecan arm (25.9 weeks [95% confidence interval {CI}, 18.3 to 31.6]), compared to supportive care only (13.9 weeks [95% CI, 11.1 to 18.6]).[9] In a randomized Phase 3 trial of amrubicin versus topotecan as second-line treatment for patients with SCLC, amrubicin did not improve survival when compared with topotecan.[10] For second-line SCLC, the median OS was 6.7 months based on a meta analysis using 21 studies published between 1984 and 2011.[11] In summary, there is a high unmet medical need for the treatment of patients with recurrent or relapsed SCLC.

1.1.2 Rationale for Immuno-oncology Therapeutic Approaches in SCLC

An analysis of peripheral blood mononuclear cells (PBMCs) from SCLC patients has shown a higher number of T-effector cells in LD-SCLC compared to ED-SCLC subjects and long-term survivors of SCLC have a higher T-effector to T regulator ratio.[12] In a Phase 2 randomized study, phased ipilimumab (placebo plus paclitaxel/carboplatin followed by ipilimumab plus paclitaxel/carboplatin) showed improved progression free survival (PFS) versus carboplatin and paclitaxel (5.7 months vs 4.6 months, Hazard Ratio (HR) = 0.72, P = 0.05), though there was no improvement when used concurrently.[13] Nivolumab at doses of 1, 3, and 10 mg/kg has been shown to be effective against non-small cell lung cancer (NSCLC) in a Phase 1 study (N = 122) with ORR of 6%, 27%, and 17% and PFS rates at 24 weeks of 25%, 44%, and 31%.[14,15] Preliminary results in a Phase 1/2 trail with nivolumab in SCLC are provided in Section 1.1.3.2. Considering the immune response seen in SCLC patients, and the results of checkpoint inhibitors nivolumab and ipilimumab in NSCLC patients, it is reasonable to expect that nivolumab monotherapy is likely to provide benefit in second-line treatment of SCLC.

1.1.3 Rationale for Nivolumab

1.1.3.1 Mechanism of Action

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds the programmed death receptor-1 (PD-1) on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.2 PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor specific T cells in vitro. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells. Additional details are available in the Nivolumab Investigator Brochure.

1.1.3.2 Phase 1/2 Data for Nivolumab in SCLC

In a Phase 1/2 study of nivolumab with or without ipilimumab for treatment of recurrent SCLC (CA209032) subjects who were platinum sensitive or refractory, and had progressive disease were enrolled regardless of tumor PD-L1 status or number of prior chemotherapy regimens. This open-label study randomized subjects to nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks (Q2W) or nivolumab + ipilimumab (1 + 1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) IV every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W. Primary objective was ORR. Other objectives were safety, PFS, OS and biomarker analysis. Seventy-five subjects were enrolled (nivolumab, n = 40; nivolumab + ipilimumab, n = 35); 59% had at least 2 prior regimens. Drug-related adverse events (AEs) in ≥ 10% of subjects were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with nivolumab; and fatigue (29%), diarrhea (17%), pruritus (14%), nausea, endocrine disorders and rash (11% each) with nivolumab + ipilimumab. Grade 3/4 drug-related AEs with nivolumab occurred in 7 (18%) subjects (all in n = 1 [3%]: stomatitis, fatigue, hyperglycemia, ALT increased, GGT increased, encephalitis, infusion related reaction).Grade 3/4 drug-related AEs in ≥ 5% included diarrhea and rash (6% each; nivolumab + ipilimumab). Drug-related pneumonitis occurred in 2 pts (1 per arm). Limbic encephalitis was reported in 2 subjects in the nivolumab arm and 1 subject in the nivolumab + ipilimumab arm. The event resolved under steroid treatment in 2 subjects and continued despite immunosuppressive treatment in 1 subject. Of 40 evaluable subjects treated with nivolumab, partial response (PR) was seen in 6, 15% (duration of ongoing responses [DOR] 80 - 251+ days); stable disease (SD) in 9, 22.5%; and progressive disease (PD) in 25, 62.5%. In conclusion, in this PD-L1 unselected heavily pretreated SCLC population including platinum based first-line treatment, nivolumab treatment was well tolerated. The ORR was 15% for subjects with nivolumab with long lasting responses beyond 251 days, all ongoing at the time of the data cut off.

1.1.3.3 Safety Profile of Nivolumab Monotherapy

In clinical trials, nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, renal cell carcinoma (RCC), NSCLC, and lymphomas. The

two clinical trials that have contributed the most to the clinical experiences of nivolumab monotherapy are studies CA209003 and CA209037. Overall, the safety profile is quite similar between these two studies and is discussed further in the sections below.

CA209003 is a completed Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg IV Q2W, up to a maximum of 2 years of total therapy. A total of 306 subjects were treated with nivolumab in the dose range of 0.1 to 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects had at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3 - 4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%). Drug related SAEs occurred in 11.5% of subjects. Grade 3 - 4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%).

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. Overall, the safety profile at 3 mg/kg (n = 54) was similar to safety profile across the dose ranges from 0.1 mg/kg to 10 mg/kg (n = 306).

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

CA209037 is an ongoing Phase 3, open-label study of nivolumab (3 mg/kg IV Q2W) vs investigator's choice therapy in subjects with previously-treated advanced melanoma. As of 30-Apr-2014, 268 subjects have been treated with 3 mg/kg IV nivolumab in CA209037 with

safety results as outlined below (source document interim CSR, DCN930081508) that are consistent with the Phase 1 experience of CA209003.

In CA209037, nivolumab-related AEs of any grade occurred in 67.5% of subjects. Of the 268 subjects treated with nivolumab, 255 (95.1%) subjects had at least 1 reported AE regardless of causality. The most frequently reported treatment-related AEs were fatigue (25.0%), pruritus (16.0%), diarrhea (11.2%), and nausea (9.3%). Most treatment-related AEs were low grade. Treatment -related high grade (Grade 3 - 4) AEs were reported in 24 (9.0%) of subjects. The most common treatment-related high grade AEs were fatigue (0.7 %), anemia (0.7%), diarrhea (0.4%), and vomiting (0.4%). Drug-related SAEs occurred in 4.5% of subjects. Grade 3 - 4 drug related SAEs reported in at least 2 subjects included diarrhea (2 subjects, 0.7%). In addition, drug related SAE of hyperglycemia occurred in 0.7%.

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) were:

- Skin (29.1%) including pruritus (16.0%) and rash (9.3%)
- GI (11.6%) including diarrhea (11.2%) and colitis (1.1%)
- Endocrine (7.8%) including hypothyroidism (7.8%) and hyperthyroidism (1.9%)
- Hepatic (4.5%) including AST increased (4.1%) and ALT increased (2.6%)
- Pulmonary (2.2%) including pneumonitis (1.9%)
- Hypersensitivity/infusion reaction (1.9%)
- Renal (1.5%) including increased creatinine (0.7%), increased urea (0.4%), and tubulointerstitial nephritis (0.4%).

In general, these select AEs were considered by the investigator to be related to study drug, except for AEs in the hepatic and renal select AE categories. There were few high-grade select AEs (n = 20), and the majority of high-grade events (13 of 20) subsequently resolved, including those for which immunosuppressive therapy was not initiated.

Treatment-related AEs leading to discontinuation were reported in 6 (2.2%) of the 268 treated subjects in CA209037 including single events of colitis, pancreatitis, increased ALT, increased lipase, autoimmune neuropathy, and demyelination. There were no deaths due to drug related toxicity in CA209037; however, 1 subject experienced drug-related Grade 5 hypoxia, possibly pneumonitis, in the setting of lymphangitic spread and possible pneumonia.

Taken together, these data from studies from CA209003 and CA209037 highlight the acceptable safety profile with similar trends in AEs in the 574 subjects treated with nivolumab in these 2 studies. Available safety data in SCLC subjects as described in Section 1.1.3.2 do not hint towards a different safety profile in SCLC compared to the tumor types investigated in studies CA209003 and CA209037. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

1.1.3.4 Standard of Care for the Treatment of Relapsed or Recurrent SCLC

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease[16] The National Comprehensive Cancer Network (NCCN) guidelines recommend for second- or later-line treatment enrollment in a clinical trial. For patients with a relapse > 6 months after completion of the first-line treatment, the original treatment regimen can be considered, although no Phase 3 study has proven an overall survival benefit of this approach. Other single agent chemotherapy options include paclitaxel, docetaxel, topotecan, irinotecan, temozolomide, gemcitabine, ifosfamide, vinorelbine, etoposide, or CAV (cyclophosphamide, doxorubicin, vincristine). All of these recommendations are category 2A per NCCN categories of evidence and consensus, except for the treatment of patients with a relapse > 2 to 3 months up to 6 months post completion of first-line treatment, where topotecan has a Phase 3 proven overall survival advantage and a category 1 recommendation. Similarly, the ESMO SCLC clinical practice guidelines which were also endorsed by the Japanese Society of Medical Oncology (JSMO) recommend a clinical trial participation for refractory patients and resistant patients with early relapse (< 6 weeks), topotecan for patients having resistant or sensitive relapse with CAV being an alternative option, and for patients with sensitive relapse reintroduction of the first-line regimen.[17] Amrubicin is approved in Japan for the treatment of SCLC patients.

1.1.3.5 Rationale for Use of Nivolumab Monotherapy as Experimental Agent (Arm A)

Substantial monotherapy clinical activity has been observed in ≥ second-line SCLC subjects treated in the ongoing Phase 1 study of nivolumab (CA209032). The ORR was 15% for subjects with nivolumab with long lasting responses up to 251 days, all ongoing at the time of the data cut off. The ORR with topotecan in a second-line SCLC Phase 3 trial was 16.9%, however, the response duration only 4.2 months, at 6 months all but one patient had progressed. Although the ORR with nivolumab in the heavily pretreated SCLC subjects is in the same range as the ORR under topotecan therapy, the response duration for subjects treated with nivolumab indicates toward a potential overall survival benefit in a Phase 3 trial. The use of nivolumab monotherapy for the experimental arm appears to be justified.

1.1.4 Rationale to Support Topotecan and Amrubicin as Comparators (Arm B)

As described in Section 1.1.3.4, topotecan is the only treatment with proven overall survival benefit in a larger randomized trial and recommended by NCCN and ESMO treatment guidelines for patients with platinum resistant and sensitive disease with a relapse less than 6 months post completion of first-line treatment. The recommendation to reintroduce the first-line regimen for patients with a disease relapse more than 6 months post first-line treatment completion is not based on a Phase 3 randomized trial actually showing improved overall survival. Therefore, it is justified to use topotecan in Study CA209331 also as a control agent for subjects with a longer than 6 months treatment free interval. Topotecan is approved in the US and Europe for the second-line treatment of platinum resistant and sensitive patients. Oral topotecan was found to demonstrate similar efficacy and safety to IV topotecan in a randomized Phase 3 study, and will

be permitted in CA290331.[18] Amrubicin is approved for the treatment of SCLC patients in Japan and commonly used in this setting. In a Phase 2 study with amrubicin the response rate in SCLC patients was 75.8% (25/33 patients).[19] Topotecan and amrubicin are considered suitable comparators given that they are the only approved second-line treatments for SCLC in the EU, US, and Japan, respectively.

1.1.4.1 Topotecan and Amrubicin Safety Profile

The safety profile of topotecan and amrubicin is characterized mainly by myelotoxicity (Table 1.1.4.1-1).

Table 1.1.4.1-1: Most Common Grade > 3 Treatment-emergent Adverse Events (Occurring in > 5% of Patients)

	Amrubicin (N = 408)		Topotecan (N = 197)	
Adverse Event	**No.**	**%**	**No.**	**%**
Hematologic				
Anemia	65	15.9	60	30.5
Febrile neutropenia	41	10.0	6	3.0
Leukopenia	62	15.2	43	21.8
Neutropenia	169	41.4	106	53.8
Thrombocytopenia	86	21.1	107	54.3
Nonhematologic				
Dyspnea	18	4.4	13	6.6
Fatigue	43	10.5	24	12.2
Hyponatremia	21	5.1	11	5.6
Infections	64	15.7	19	9.6
Pneumonia	27	6.6	6	3.0

Source: Adapted from Von Pawel et al, JCO, Dec 2014[10]

1.1.5 Rationale for Open-label Study Design

This study will use an open-label design. Due to the obvious difference in chemotherapy and immunotherapy related toxicities, the different schedules and durations of therapy in the treatment arms, different dose modification rules for safety management, and different premedication requirements according to chemotherapy, an open-label design is appropriate. An open-label design will also help ensure that immune-related toxicities in subjects receiving immunotherapy are promptly identified and managed.

1.1.6 Rationale to Support Nivolumab Monotherapy Flat Dose (Arm A)

Nivolumab monotherapy has been extensively studied in NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057 with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected in these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients. Table 1.1.6-1 presents summary statistics of the estimated nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) in NSCLC subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat nivolumab dose of 240 mg. It should be noted that a dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 clinical studies of nivolumab monotherapy in NSCLC patients (CA209017, CA209057, and CA209063). As evident from the data presented in Table 1.1.6-1, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Table 1.1.6-1: Summary Statistics of Nivolumab Steady-state Exposure

Nivolumab Dose	Cminss Geo. Mean [ug/mL] (cv%)	Cmaxss Geo. Mean [ug/mL] (cv%)	Cavgss Geo Mean [ug/mL] (cv%)
240 mg	61.5 (44.6)	133.7 (35.0)	84.2 (38.2)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

Based on these clinical results, the experimental arm in CA209331 will be nivolumab monotherapy 240 mg Q2W for subjects with relapsed SCLC.

1.1.7 Rationale for Shorter Infusion Times for Nivolumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration will diminish the burden provided no change in safety profile.

Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration for nivolumab (1 - 3 mg/kg). However, nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

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

1.1.8 Rationale for Collection of Tumor Tissue and Evaluation of Tumor PD-L1 Expression and Tumor Mutational Burden as Potential Predictive Biomarkers

The role of PD-L1 as a potential predictive biomarker in SCLC is unknown. Preliminary internal data from SCLC tumor samples show that less than 10% of tumor samples have ≥ 5% PD-L1 positive tumor cells. A preliminary analysis of tumor samples in Study CA209032 showed no suggestion of a correlation of PD-L1 expression and tumor shrinkage under nivolumab therapy. Recently, expression of PD-L1 was shown to be positively correlated with a LD stage, and to be an independently predictive factor of a favorable overall survival versus PD-L1-negative tumors.[20]

In order to more thoroughly assess the role of PD-L1 protein expression as a predictive biomarker in SCLC, archival or recent tumor tissue will be collected prospectively from all randomized subjects in this study, and a retrospective analysis of efficacy by PD-L1 expression status will be conducted. Subjects enrolled to CA209331 will not be selected or stratified by PD-L1 expression status. However, based on preliminary PD-L1 prevalence estimates in SCLC a reasonable number of PD-L1 positive subjects are anticipated to accrue to each treatment arm for an exploratory analysis.

In addition, tumor mutational burden will be evaluated as an independent predictive biomarker for efficacy, following recently presented data from the CA209032 SCLC cohort,[21] as part of the exploratory analyses.

1.1.9 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in a Phase 1 study of nivolumab[14] and also in combination with ipilimumab.[22] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors

could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore subjects randomized to nivolumab monotherapy will be allowed to continue study therapy after initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST 1.1) defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.5.4). Such subjects must discontinue study therapy upon evidence of further progression.

1.2 Research Hypothesis

Treatment with nivolumab will increase OS as compared with chemotherapy in subjects with relapsed SCLC treated with prior platinum-based, first-line chemotherapy.

1.3 Objectives(s)

1.3.1 Primary Objectives

To compare the OS of nivolumab versus chemotherapy in subjects with relapsed SCLC after platinum-based, first-line chemotherapy.

1.3.2 Secondary Objectives

Secondary objectives are:

- To compare the PFS of nivolumab versus chemotherapy
- To compare the ORR of nivolumab versus chemotherapy.

1.3.3 Exploratory Objectives

The exploratory objectives are:

- To evaluate the safety and tolerability of nivolumab versus chemotherapy
- To characterize pharmacokinetics of nivolumab and explore exposure response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints
- To explore PD-L1 expression as an independent predictive biomarker for OS, ORR, or PFS in nivolumab and chemotherapy groups
- To explore tumor mutational burden expression as an independent predictive biomarker for efficacy in nivolumab and chemotherapy groups
- To correlate potential predictive biomarkers in peripheral blood and tumor specimens, including proteins involved in regulating immune responses (eg, [redacted], PD-L1, [redacted]), mutational as well as immunohistochemistry (IHC) spectrum, with endpoints such as ORR, PFS and OS in nivolumab and chemotherapy groups
- [redacted]

- To characterize immunogenicity of nivolumab
- To evaluate the proportion of subjects with meaningful symptom deterioration by 12 weeks and by 24 weeks, as measured using the Lung Cancer Symptom Scale (LCSS) average symptom burden index (ASBI), between nivolumab and chemotherapy groups
- To evaluate the time to symptom deterioration (TTSD), as measured by the average symptom burden index (ASBI) of the Lung Cancer Symptom Scale (LCSS), in subjects receiving nivolumab versus chemotherapy
- To assess the subject's overall health status using the EQ-5D index and visual analog scale in nivolumab and chemotherapy groups.

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with NSCLC, RCC, glioblastoma and other cancer types. Recently, nivolumab was approved for the treatment of patients with advanced squamous NSCLC and melanoma.

In a Phase 1/2 trial in subjects with heavily pretreated SCLC, nivolumab monotherapy showed an ORR of 15%.[23] Study CA209331 will be the first Phase 3 study in the clinical development program for SCLC and will evaluate the efficacy and safety of nivolumab monotherapy, as second-line therapy, in subjects with relapsed SCLC after platinum-based first-line chemotherapy.

1.5 Overall Risk/Benefit Assessment

Subjects with SCLC who relapse or progress after platinum based first-line therapy represent a great unmet medical need. Responses to salvage chemotherapy are short lived and the overall survival benefit of chemotherapy is modest. The clinical activity of nivolumab monotherapy observed to date in SCLC suggests the potential for improved clinical outcomes relative to approved chemotherapy. However, nivolumab has not been directly compared to any approved chemotherapy in SCLC previously. Topotecan, the only approved 2nd line treatment for SCLC in the US and Europe, has a well characterized AE profile consistent with cytotoxic chemotherapy, such as pancytopenia including febrile neutropenia, nausea, fatigue, vomiting, stomatitis, fever, and diarrhea. Amrubicin is approved for SCLC in Japan and its safety profile is characterized as well by pancytopenia including febrile neutropenia. Nivolumab can cause clinically relevant AEs including liver toxicities, thyroiditis, pneumonitis, and diarrhea. The activity and manageable AE profile observed with nivolumab supports a head-to-head evaluation versus chemotherapy in second-line SCLC. To assure an ongoing favorable benefit-risk assessment for subjects enrolled onto CA209331, an independent Data Monitoring Committee (DMC) will be utilized to monitor the activity and safety of nivolumab versus chemotherapy throughout the conduct of the trial.

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 Bristol-Myers Squibb (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.

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

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

Investigators must:

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 Health Insurance Portability and Accountability Act (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 a randomized, open-label, two-arm, multicenter, Phase 3 study in adult subjects with relapsed SCLC treated with prior platinum-based, first-line chemotherapy. Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than

4 cycles, they must have had a best overall response (BOR) of a partial or complete response after completion of chemotherapy.

Approximately 480 subjects will be randomized in a 1:1 ratio to treatment with either nivolumab (Arm A) or chemotherapy (either topotecan or amrubicin, Arm B) in the Global Population. In addition, this study includes a cohort of at least 78 additional randomized patients from China (~ 16% of the global number of randomized subjects). The primary population for safety and efficacy analysis will include subjects from the Global Population as well as subjects from the additional China cohort, leading to a total sample size of about 560 subjects.

Subjects will be stratified according to the following factors:

- Response to first-line platinum based treatment: platinum sensitive (progression-free interval ≥ 90 days after completion of platinum therapy) vs platinum resistant (progression-free interval < 90 days after completion of platinum therapy)
- Brain metastases at baseline: yes vs no.

Treatments will be administered as follows:

Arm A:

- Nivolumab 240 mg (flat dose) on Day 1 of a 14-day cycle as an IV infusion over 30 minutes.

Arm B:

- Topotecan: 1.5 mg/m^2 administered as 30-minute IV infusion or 2.3 mg/m^2 administered as an oral capsule (round dose to nearest 0.25 mg) once daily on Days 1 to 5 of a 21-day cycle.
- Amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC treatment): 40 mg/m^2 administered as 5-minute IV infusion once daily on Days 1 to 3 of a 21-day cycle.

On-study tumor assessments will begin at Week 6 post randomization (± 5 days) and be performed every 6 weeks (± 5 days) until Week 30. After Week 30, tumor assessments will be performed every 12 weeks (± 5 days) until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond investigator-assessed progression [Section 4.5.4]), lost to follow-up, withdrawal of study consent, or the study ends.

Enrollment will end after approximately 560 subjects have been randomized (including ~78 additional subjects in China).

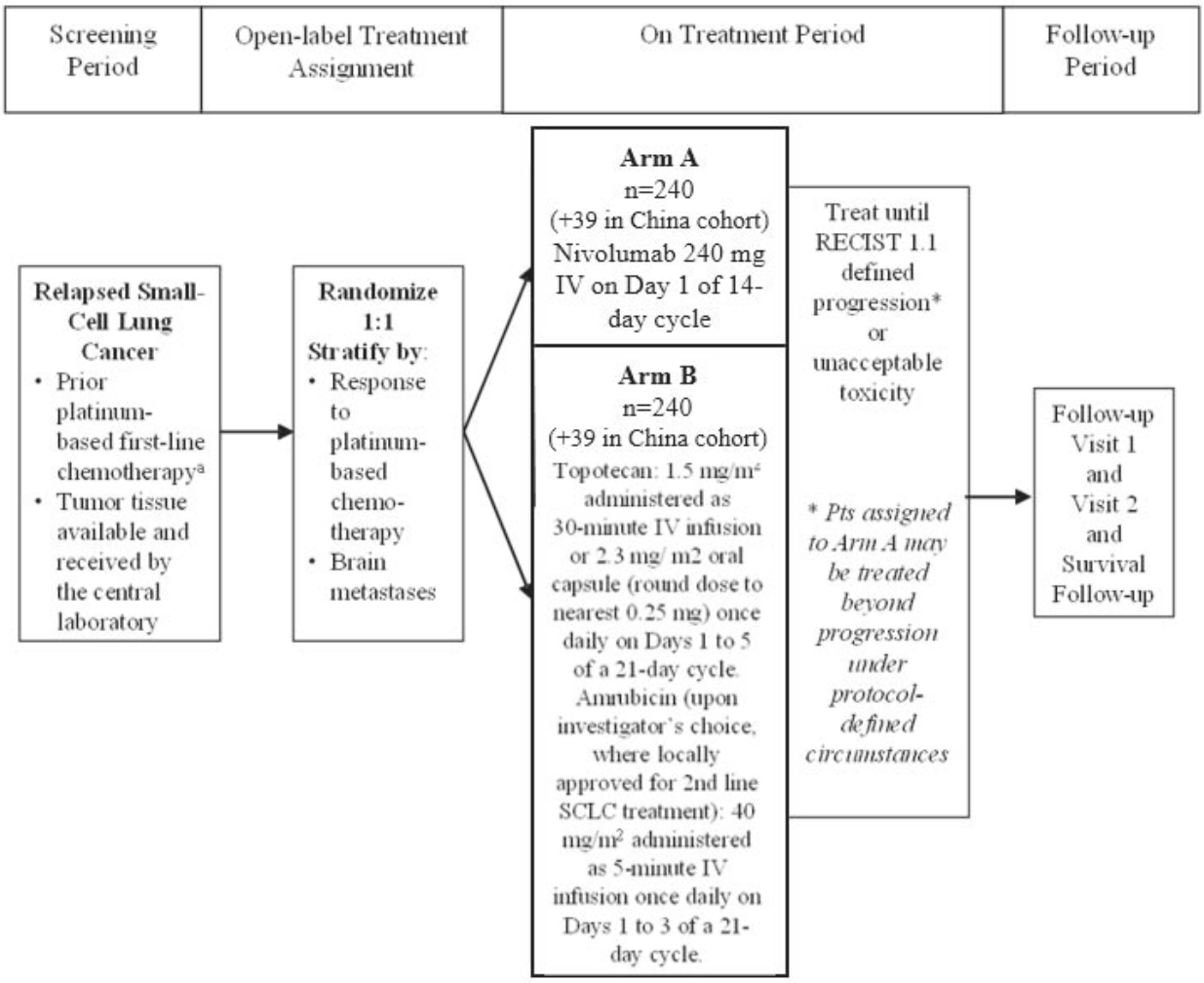
The primary endpoint of the study is OS.

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

Accrual duration is expected to be approximately 18 months; overall study duration will be approximately 34 months (18 months accrual + minimum follow up of 16 months). The study will end when analysis of survival is complete. Additional survival follow-up may continue for up to 5 years from the time of this analysis.

A DMC will be utilized to provide general oversight and safety considerations for this study, CA209331 (Section 7).

Figure 3.1-1: Study Schematic



[a] Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than 4 cycles of platinum-based first-line chemotherapy, they must have had a best overall response (BOR) of at least a partial or complete response after completion of chemotherapy.

3.1.1 Study Phases

The study is divided into the following phases: Screening, Treatment, and Follow-up

3.1.1.1 Screening

- Screening begins after the subject signs the informed consent form (ICF). Subjects will undergo screening evaluations to determine eligibility.

- Tumor tissue (archival or recent tumor biopsy) must be available and received by the central lab for correlative studies in order 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.
- Baseline disease or tumor assessments should be performed within 28 days of randomization.
- The screening phase either ends with confirmation of full eligibility and randomization of the subject or with the confirmation that the subject is a screen failure.

Subject is assessed for study eligibility as described in Table 5.1-1.

3.1.1.2 Treatment

- The treatment phase begins with the randomization call to the interactive voice response system (IVRS). The subject is randomly assigned to one of the 2 treatment arms. Treatment should begin within 3 business days of randomization.
- Study drug is administered as an IV infusion or oral capsule beginning on Treatment Day 1 of each cycle (frequency is dependent on the treatment arm) until disease 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. Radiographic assessments will be obtained in all treatment arms at Week 6 (± 5 days) and every 6 weeks from Week 6 (± 5 days) for the first 30 weeks, and subsequently every 12 weeks (± 5 days), until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends.
- Subjects in Arm A may continue treatment beyond investigator-assessed RECIST 1.1-defined progression as defined in Section 4.5.4.
- This phase ends when the subject is discontinued from study drug.

Study assessments are to be collected as outlined in Table 5.1-2 or Table 5.1-3 for subjects randomized to nivolumab monotherapy or chemotherapy, respectively.

3.1.1.3 Follow up

- Begins when the decision to discontinue a subject from study drug is made (no further treatment with study drug).
- Follow-up consists of 2 follow-up visits within approximately 100 days of the last dose of study drug followed by survival visits that will continue every 3 months after Follow-up Visit 2 until death, lost to follow-up, or withdrawal of study consent.
- Subjects who discontinue study drug for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 5 days) for the first 30 weeks, and subsequently every 12 weeks (± 5 days), until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends.

Study assessments are to be collected as outlined in Table 5.1-4.

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) Histologically or cytologically confirmed SCLC.

b) Subjects with either limited or extensive disease stage at the initial diagnosis are eligible.

c) Must have recurrence or progression after platinum-based, first-line chemotherapy or chemoradiation therapy for the treatment of limited or extensive disease stage SCLC:

i) Subjects must have received at least 4 cycles of platinum-based, first-line chemotherapy for either limited or extensive stage disease or if they received less than 4 cycles, they must have had a best overall response (BOR) of a partial or complete response after completion of chemotherapy.

ii) Subjects must have had only 1 prior regimen of platinum-based, first-line treatment. Subjects receiving maintenance therapy following platinum-based, first-line treatment are excluded.

d) Evaluable disease by CT/MRI per RECIST 1.1 criteria (Appendix 2).

e) Subject must have demonstrated disease progression based on at least one tumor assessment done after completion of chemotherapy and prior to randomization. The tumor assessment performed during screening will be used as a baseline for efficacy assessments.

f) A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.6.1. Specimens must be received by the central laboratory prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.

g) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

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. Only the screening procedures performed outside of the protocol specified timing (eg, > 28 days) must be repeated.

i) Any prior radiotherapy, including radiosurgery to metastases of the brain must have been completed at least 2 weeks prior to randomization.

3. Age and Reproductive Status

a) Males and females, ≥ 18 to 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 beta-human chorionic gonadotrophin) 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 with plus 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion (for subjects treated in Arm A).

   WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment plus 5-half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received , whichever is longer (for subjects treated with 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 nivolumab plus 90 days (duration of sperm turnover) for a total of 7 months post treatment completion (for subjects treated in Arm A).

   Males who are sexually active with WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy 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 use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

- Progestogen only hormonal contraception associated with inhibition of ovulation.
- Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
- Nonhormonal IUDs, such as ParaGard®
- Bilateral tubal occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure
    - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Intrauterine hormone-releasing system (IUS).
- Complete abstinence*
    - *Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms).
    - Complete abstinence is an acceptable form of contraception for all study drug and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests as specified in Section 6.4.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

MALE SUBJECTS WITH PARTNERS WHO ARE WOCBP:

Are required to use condoms, in addition to the requirement for their female partners who are WOCBP to use a highly effective method of contraception listed above

UNACCEPTABLE METHODS OF CONTRACEPTION

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)
- Vaginal sponge
- progestin only pills
- cervical cap with spermicide
- a male and female condom must not be used together.

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

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

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

2. Medical History and Concurrent Diseases

a) Not applicable

b) Documented carcinomatous meningitis

c) Active, known or suspected autoimmune disease. Subjects with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment are excluded. However, 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.

d) A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. However, corticosteroids with minimal systemic absorption (inhaled or topical steroids 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

e) 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)

f) Prior treatment with topotecan or amrubicin

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

h) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have been resolved to grade 1 (National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI CTCAE] version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and resulted in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll

i) Other active malignancy requiring concurrent intervention

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

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

l) Treatment with any chemotherapy, biologics for cancer, or investigational therapy within 28 days of first administration of study drug (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to CTC grade 1 level)

m) Major surgery or significant traumatic injury that is not recovered at least 14 days before the first dose of study drug

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBVsAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection. Subjects with a positive test for HCV antibody but no detection of HCV RNA indicating no current infection are eligible.

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

c) Inadequate hematologic function defined by:

i) White blood cells (WBCs) < 2000/mm^3

ii) Absolute neutrophil count (ANC) < 1500/mm^3, or

iii) Platelet count < 100,000/mm^3, or

iv) Hemoglobin level < 9 g/dL.

d) Inadequate hepatic function as defined by either:

i) Total bilirubin level ≥ 2.5 times the ULN, or

ii) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≥ 2.5 times the ULN or ≥ 5 times the ULN if liver metastases are present.

e) Creatinine Clearance (Cockcroft-Gault) < 20 mL/min

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to any of the study drugs or study drug components

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.

3.3.3 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

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE or an autoimmune paraneoplastic syndrome). Subjects with an autoimmune paraneoplastic syndrome at enrollment requiring concurrent immunosuppressive treatment are not eligible.
- Systemic corticosteroids > 10 mg daily prednisone equivalent, except as stated in Section 3.4.3 or to treat a drug-related AE.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer or radiation therapy, except for palliative radiation therapy described in Section 3.4.2). On study radiation treatment to brain metastases is not permitted.
- Surgical resection of tumor.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with nivolumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged.

3.4.2 Other Restrictions and Precautions

Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy while on study treatment. Details of palliative radiotherapy should be documented in the source records and case report form (CRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

Subjects requiring palliative radiotherapy should be assessed for disease progression. Subjects considered as having progressive disease are required to discontinue study therapy, or in Arm A, if appropriate, continue nivolumab therapy as treatment beyond progression. Administration of additional nivolumab to subjects who experienced disease progression at the time of palliative radiotherapy should follow guidelines specified in Section 4.5.4 Treatment Beyond Disease Progression.

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 including doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

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

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is an allowed therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomization per inclusion criterion 2i) in Section 3.3.1. See Section 3.4.2 for guidance on concomitant palliative radiotherapy.

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:

- Disease progression as assessed by RECIST 1.1 criteria (Appendix 2), unless the subject is assigned to the nivolumab treatment arm and meets criteria for treatment beyond progression (Section 4.5.4).
- Subject's request to stop study treatment
- Any clinical 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 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 specified reasons for discontinuations, see Section 4.5.3.

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 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. 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). All study drugs are listed in Table 4-1.

Table 4-1: Study Drugs for BMS-936558 - Treatment Phase					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open Label**	**Packaging/ Appearance**	**Storage Conditions (per label)**
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open Label	10 mL per vial/ 5 or 10 vials per box Vials contain clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing
Topotecan hydrochloride concentrate for solution for infusion[b]	4 mg (1 mg/mL)	IP	Open Label	4 mg per vial/ 1 or 5 vials per box Vials contain clear yellow to yellow/green solution	Store at 2° to 8°C. Protect from freezing and light. Store in outer carton.
Topotecan hydrochloride powder for infusion[b]	TBC	IP	Open Label	TBC	Store at 15° to 25°C. Protect from freezing and light. Store in outer carton.
Topotecan capsule[b]	0.25 mg/ 1 mg	IP	Open Label	TBC	Store at 2° to 8°C. Protect from freezing and light. Store in outer carton.
Amrubicin hydrochloride powder for solution for injection[b]	50 mg	IP	Open Label	50 mg per vial/ 1 vial per box Vials contain yellow-red powder or mass	Store at 15° to 25°C.

[a] Labeled as either “BMS-936558-01” or “Nivolumab”

[b] For sites/countries in which the marketed product of topotecan and/or amrubicin, will be procured locally, the potency, packaging configuration and storage conditions 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) are:

- Nivolumab
- Topotecan
- Amrubicin

4.1.1 Nivolumab

Nivolumab 240 mg (flat dose) on Day 1 of a 14-day cycle as an IV infusion over 30 minutes. Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, preparation, and administration information for nivolumab.

4.1.2 Topotecan

Topotecan: 1.5 mg/m^2 administered as 30-minute IV infusion or 2.3 mg/m^2 administered as an oral capsule (round dose to nearest 0.25 mg) once daily on Days 1 to 5 of a 21-day cycle. Please refer to the current version of the Summary of Product Characteristics (SmPC), US Package Insert (USPI), or other country-specific labeling and/or pharmacy reference sheet for complete storage, handling, preparation, and administration information for topotecan.

4.1.3 Amrubicin

Amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC treatment): 40 mg/m^2 administered as 5-minute IV infusion once daily on Days 1 to 3 of a 21-day cycle. Please refer to the current version of the country-specific labeling and/or pharmacy reference sheet for complete storage, handling, preparation, and administration information for amrubicin.

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: any pre-medications associated with the comparator arms and medications used to treat chemotherapy infusion-related reactions. Also, any medications used to treat nivolumab infusion-related reactions (eg. steroids). These non-

investigational products should be sourced by the investigator sites if available and permitted by local regulations.

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.

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

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

4.4 Method of Assigning Subject Identification

4.4.1 Screening

After informed consent has been obtained, the subject must be enrolled into the study by calling an interactive IVRS to obtain the subject number. The following information is required for subject registration:

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

4.4.2 Randomization

Once a subject has been determined to meet eligibility criteria, site personnel will make another call to the IVRS. The following information is required for subject randomization:

- Subject number
- Confirmation that all randomization inclusion/exclusion are met
- Confirmation that FFPE tumor tissue block or unstained slides were received by the central laboratory
- Response to first-line platinum-based treatment: platinum sensitive vs platinum resistant
- Brain metastases at baseline: yes vs no.

If the above are met, the IVRS will randomly assign subjects to treatment Arm A or Arm B in a 1:1 ratio using a stratified permuted block randomization method with respect to the following stratification factors:

- Response to first-line platinum based treatment: platinum sensitive vs platinum resistant
- Brain metastases at baseline: yes vs no.

The first dose of study drug is to be administered within 3 business days following randomization.

Randomization will be performed based on a randomization schedule generated and maintained by the Randomization Group within Bristol-Myers Squibb.

The procedures for using the IVRS will be detailed in a separate document.

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Dosing Schedule

The dosing schedule is detailed below Table 4.5.1-1.

Table 4.5.1-1: Dosing Schedule

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Arm A						
Nivolumab 240 mg[a] q 2 weeks	Day 1 Nivolumab		Day 1 Nivolumab		Day 1 Nivolumab	
Arm B						
Topotecan[a] IV 1.5 mg/m^2 or capsule 2.3 mg/m^2 or	Day 1 - 5 Topotecan			Day 1 - 5 Topotecan		
Amrubicin[a] 40 mg/m^2	Day 1 - 3 Amrubicin			Day 1 - 3 Amrubicin		

[a] Treatment continues until disease progression (or until discontinuation of study drug in subjects receiving nivolumab), discontinuation due to toxicity, withdrawal of consent, or the study ends.

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and AE criteria, as described in Sections 4.5.2 and 4.5.3.

4.5.1.1 Nivolumab

For subjects randomized to Arm A, nivolumab will be administered as a flat dose of 240 mg on Day 1 of a 14-day cycle as an IV infusion over 30 minutes. The rationale for this dosage schedule is provided in Section 1.1.6.

Refer to the Pharmacy Information sheets for more detail. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.5.

Dosing Window: Subjects may be dosed no less than 12 days between doses and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks after the delayed dose.

A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor, as described in Section 4.5.3.1.

Management Algorithms for Immuno-Oncology Agents

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

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological.

The algorithms are found in the Investigator Brochure and Appendix 1 of this protocol.

Changes in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 criteria. Please refer to Appendix 2 for the specifics of the RECIST 1.1 criteria to be utilized in this study.

4.5.1.2 Topotecan

Subjects randomized to Arm B will receive treatment with topotecan 1.5 mg/m^2 IV infusion or 2.3 mg/m^2 oral capsule (round dose to nearest 0.25 mg) on Days 1 through 5 every 3 weeks (21 days). Refer to the local product label for more details.

Dosing Window: Subjects may be dosed no less than 14 days from the last dose of the previous cycle and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 3 weeks after the delayed dose.

A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor, as described in Section 4.5.3.1.

4.5.1.3 Amrubicin

Subjects randomized to Arm B will receive treatment with amrubicin 40 mg/m^2 on Days 1 through 3 every 3 weeks (21 days). Refer to the local product label for more detail.

Dosing Window: Subjects may be dosed no less than 16 days from the last dose of the previous cycle and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 3 weeks after the delayed dose.

A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor, as described in Section 4.5.3.1.

4.5.2 Dose Modifications and Dose Delays

This section includes information on dose modifications, dose delays, and provides guidelines for resuming treatment after a dose delay. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

4.5.2.1 Nivolumab

No dose modifications of nivolumab are allowed for the management of toxicities experienced by individual subjects.

Dose delay criteria apply for all drug-related AEs. Treatment delays up to 6 weeks (42 days) from the last dose are allowable.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipasedoes not require dose delay
    - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 4.5.3.1)
- 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 criteria are met

Criteria to Resume Treatment

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, 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 4.5.3.1) 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 regardless of control with hormone replacement

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol.

If treatment is delayed > 6 weeks (42 days) from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.3.1.

4.5.2.2 Topotecan

Dose modifications and dose delays for the management of toxicities experienced by individual subjects in Arm B who are receiving topotecan are provided in Table 4.5.2.2-1. In addition, treatment may be delayed for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Table 4.5.2.2-1: Topotecan Dose Modifications and Delays	
Adverse Event	**Dose Modification**
ANC < 1000/mm^3 and/or Platelets < 100,000/mm^3 at Day 1	Delay treatment until: ANC ≥ 1000/mm^3 Platelets > 100,000/mm^3
Toxicity Grade < 2 during previous cycle	Optional, based on local treatment guidelines: Increase IV topotecan dosage to a maximum of 2 mg/m^2 per day in increments of 0.25 mg/m^2 per day. Increase oral topotecan dosage to a maximum of 3.1 mg/m^2 in increments of 0.4 mg/m^2 per day.
Grade 4 neutropenia with fever or infection, or of duration ≥ 7 days Grade 3 neutropenia during the preceding cycle persisting after Day 21 Grade 4 thrombocytopenia	Reduce IV topotecan dosage by 0.25 mg/m^2 per day. Reduce oral topotecan dosage by 0.4 mg/m^2 per day.
Grade 3/4 Nonhematologic toxicity, excluding Grade 3 nausea	Reduce IV topotecan dosage by 0.25 mg/m^2 per day or discontinue treatment. Reduce oral topotecan dosage by 0.4 mg/m^2 per day or discontinue treatment.
Treatment delay > 6 weeks	Discontinue treatment

ANC = absolute neutrophil count

Note: The minimum permissible daily IV topotecan dosage is 1 mg/m^2; the minimum daily oral topotecan dosage is 1.5 mg/m^2.

Criteria to Resume Treatment

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

- Treatment can be resumed when ANC ≥ 1000/mm^3 and platelets > 100,000/mm^3
- 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
- Drug-related pulmonary toxicity must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol.

If treatment is delayed > 6 weeks (42 days) from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.3.2.

When resuming topotecan treatment, please follow the dose reduction recommendations noted in Table 4.5.2.2-1.

4.5.2.3 Amrubicin

Dose modifications and dose delays for the management of toxicities experienced by individual subjects in Arm B who are receiving amrubicin are provided in Table 4.5.2.3-1. In addition, treatment may be delayed for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Table 4.5.2.3-1: Amrubicin Dose Modifications

Amrubicin: Dose Modifications and Delays	
Adverse Event	**Dose Modification**
ANC < 1000/mm^3 and/or Platelets < 100,000/mm^3 at Day 1	Delay treatment until: ANC ≥ 1000/mm^3 Platelets ≥ 100,000/mm^3
Grade 4 neutropenia with fever or infection, or of duration ≥ 7 days Grade 3 neutropenia during the preceding cycle persisting after Day 21 Grade 4 thrombocytopenia	Reduce amrubicin dosage by 5 mg/m^2 per day
Grade 3/4 Nonhematologic toxicity, excluding Grade 3 nausea	Reduce amrubicin dosage by 5 mg/m^2 per day
Treatment delay > 6 weeks	Discontinue treatment

ANC = absolute neutrophil count

Criteria to Resume Treatment

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

- Treatment can be resumed when ANC ≥ 1000/mm^3, and platelets ≥ 100,000/mm^3
- 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
- Drug-related pulmonary toxicity must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol.

If treatment is delayed > 6 weeks (42 days) from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.3.3.

When resuming amrubicin treatment, please follow the dose reduction recommendations noted in Table 4.5.2.3-1.

4.5.3 Discontinuation Criteria

4.5.3.1 Nivolumab

Treatment with nivolumab 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, neurologic toxicity, hypersensitivity reactions, infusion reactions and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration 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

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin) except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents,

respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any event that leads to delay in dosing lasting > 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.

Tumor assessments for all subjects should continue as per protocol even if study drug dosing is interrupted.

4.5.3.2 Topotecan

Treatment with topotecan should be permanently discontinued for the following:

- Confirmed new diagnosis of interstitial lung disease (ILD): Topotecan has been associated with reports of ILD, some of which have been fatal. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation, and use of pneumotoxic drugs and/or colony stimulating factors. Monitor subjects for pulmonary symptoms indicative of interstitial lung disease (eg, cough, fever, dyspnea, and/or hypoxia), and discontinue topotecan if a new diagnosis of ILD is confirmed.
- Any dosing interruption lasting > 6 weeks (42 days) from the last dose.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued topotecan dosing.
- Any dosing interruption lasting > 6 weeks from the last dose with the following exception:
  - Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

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

4.5.3.3 Amrubicin

Treatment with amrubicin should be permanently discontinued for the following:

- Confirmed new diagnosis of interstitial lung disease (ILD): Amrubicin has been associated with reports of ILD, some of which have been fatal. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation, and use of pneumotoxic drugs and/or colony stimulating factors. Monitor subjects for pulmonary symptoms indicative of interstitial lung disease (eg, cough, fever, dyspnea, and/or hypoxia), and discontinue topotecan if a new diagnosis of ILD is confirmed
- Any dosing interruption lasting > 6 weeks (42 days) from the last dose.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued amrubicin dosing.
- Any dosing interruption lasting > 6 weeks from the last dose with the following exception:
  - Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

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

4.5.4 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[22]

Subjects in Arm B who were treated with topotecan or amrubicin will not be permitted to continue treatment beyond RECIST 1.1 defined initial PD.

Subjects in Arm A who were treated with Nivolumab will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Tolerating study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- 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 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.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. The subject will continue to receive monitoring according to the Time and Events Schedule on Table 5.1-2.

A radiographic assessment/ scan should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD.

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. For subjects with evaluable disease only, further progression is defined as unequivocal disease progression of non target lesions or the development of new measurable lesions from time of initial PD. Treatment should be discontinued permanently upon documentation of further disease progression.

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

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For subjects in both treatment arms, 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 of treatment.

4.5.5 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, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as a serious adverse event (SAE) if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) 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 paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF).
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 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 1:1,000 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 from symptoms.

In the 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)

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

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 Procedural Outline (CA209331)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status. Within 14 days prior to first dose
Vital Signs and Oxygen Saturation	X	Temperature, BP, HR, and O2 saturation by pulse oximetry at rest. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonates (optional), albumin, amylase or lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBVsAg), and hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), within 14 days prior to first dose. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing.
ECG, Echocardiogram (LVEF) or MUGA	X	

Table 5.1-1: Screening Procedural Outline (CA209331)

Procedure	Screening Visit	Notes
Pregnancy Test	X	Performed within 24 hours prior to first dose for WOCBP only (serum or urine - local/site)
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment	X	Contrast-enhanced CT of the chest and CT or MRI of abdomen, pelvis, and any other known sites of disease. Brain MRI or CT. Subjects with incidental brain metastases findings at screening will need to undergo radiation treatment first to be eligible. Should be performed within 28 days prior to randomization. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Collection of Tumor Tissue for Biomarker Evaluation	X	Tumor tissue obtained before randomization (formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Fine needle aspiration or cytospins are insufficient. For subjects where a biopsy is not feasible, archival tumor material must be made available. Submission of fewer than 10 unstained slides may be accepted under certain circumstances and must be approved by BMS medical monitor Specimens must be received by the central lab prior to subject randomization.
IVRS/Clinical Drug Supplies		
Phone Calls to IVRS	X	Phone calls must be made to IVRS as follows: For subject number assignment at the time informed consent is obtained. For randomization to treatment after eligibility has been confirmed, or in the event of screen failure (subject does not meet eligibility criteria).

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, CBC = complete blood count, Cl = chloride, CNS = central nervous system, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, HR = heart rate, IVRS = interactive voice response system, K = potassium, LDH = lactate dehydrogenase, Mg = magnesium, MRI = magnetic resonance imaging, Na = sodium, O2 = oxygen, P = phosphorus, T.Bili = total bilirubin, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine, WOCBP = women of childbearing potential

Table 5.1-2: On-Treatment Assessments for Subjects Randomized to Arm A, Nivolumab Monotherapy (CA209331)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (Every 2 Weeks) on Day 1 (± 3 Days)	Notes
Safety Assessments				
Targeted Physical Examination	X		X	Within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X		X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X		X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------Continuously----------			Assessed using NCI CTCAE v. 4.0. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry
Review of Concomitant Medications	X		X	
Laboratory Tests	X		X	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing for Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, etc.) and include: CBC with differential, uric acid, serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase or lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Limited on-study local laboratory assessment should be done within 72 hours prior to dosing (beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, etc.) and include: CBC with differential, LFTs (ALT, AST, t.bili, alkaline phosphatase) and creatinine.
Thyroid Function Testing			See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 1 week).

Table 5.1-2: On-Treatment Assessments for Subjects Randomized to Arm A, Nivolumab Monotherapy (CA209331)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (Every 2 Weeks) on Day 1 (± 3 Days)	Notes
Pregnancy Test	X		See Note	For WOCBP only: Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.
Efficacy Assessments				
Radiographic Tumor Assessment			See Note	CT of the chest. CT/MRI of abdomen and any other known sites of disease. Repeat CT/MRI of pelvis is required for subjects with pelvic metastases at baseline, or if clinically indicated. Subjects with a history of brain metastasis should have surveillance MRI every 6 weeks, or sooner if clinically indicated. The same methods should be used throughout the study. See Table 5.4-1 for CT/MRI scan schedule.
Pharmacokinetic (PK) and Immunogenicity Assessments				
PK samples	X		See Note	See Table 5.5-1 of PK and Immunogenicity Sampling
Immunogenicity samples	X		See Note	See Table 5.5-1 of PK and Immunogenicity Sampling

Table 5.1-2: On-Treatment Assessments for Subjects Randomized to Arm A, Nivolumab Monotherapy (CA209331)

Procedure	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 8 (C1D8)	Each Cycle (Every 2 Weeks) on Day 1 (± 3 Days)	Notes
Exploratory Biomarker Assessments				
Biomarker samples ([redacted], Whole Blood, Tumor Biopsy)	X	X	See Note	See Table 5.6-1of Biomarker Sampling Schedule
Outcomes Research Assessments				
Patient Reported Outcomes (PRO)	X		See Note	For on-study visits: Assessments (Lung Cancer Symptom Scale and EQ-5D) will be performed prior to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment phase.
Health Resource Utilization			X	Except Cycle 1. Note that concomitant medication collection will be included.
Study Drug				
Administer Study Drug	X		X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment. Note: Treatment should begin within 3 business days of randomization. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. IVRS should also be contacted at upon discontinuation of treatment.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, Cl = chloride, CNS = central nervous system, CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, HR = heart rate, IVRS = interactive voice response system, K = potassium, LDH = lactate dehydrogenase, LFT = liver function tests, Mg = magnesium, MRI = magnetic resonance imaging, Na = sodium, NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events, O2 = oxygen, P = phosphorus, SAE = serious adverse event, T.Bili = total bilirubin, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine, WOCBP = women of childbearing potential

Table 5.1-3: On-Treatment Assessments for Subjects Randomized to Arm B, Chemotherapy (CA209331)

Procedure	Cycle 1 Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) (C1D1)	Cycle 2 to x Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) C2D1 to CxD1	Notes
Safety Assessments			
Targeted Physical Examination	X	X	Within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X	X	Temperature, BP, HR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical Measurements	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	---------- Continuously ----------		Assessed using NCI CTCAE v. 4.0. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry
Review of Concomitant Medications	X	X	
Laboratory Tests	X (See Note)	X (See Note)	Extended on-study local laboratory assessments should be done within 72 hours prior to dosing and include: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate (optional), amylase or lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. In addition, the following laboratory assessments should be done: Day 15 of each cycle (optional according to local treatment guidelines): CBC with Differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Thyroid Function Testing		See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 1 week).
Pregnancy Test	X	See Note	For WOCBP only: Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.

Table 5.1-3: On-Treatment Assessments for Subjects Randomized to Arm B, Chemotherapy (CA209331)

Procedure	Cycle 1 Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) (C1D1)	Cycle 2 to x Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) C2D1 to CxD1	Notes
Efficacy Assessments			
Radiographic Tumor Assessment		See Note	CT of the chest. CT/MRI of abdomen and any other known sites of disease. Repeat CT/MRI of pelvis is required for subjects with pelvic metastases at baseline, or if clinically indicated. Subjects with a history of brain metastasis should have surveillance by MRI every 6 weeks or sooner if clinically indicated. The same methods should be used throughout the study. See Table 5.4-1 for schedule of CT/MRI assessments.
Exploratory Biomarker Assessments			
[redacted] Whole Blood Tumor Biopsy	X	See Note	See Table 5.6-2of Biomarker Sampling Schedule
Outcomes Research Assessments			
Patient Reported Outcomes (PRO)	X	See Note	For on-study visits: Assessments (Lung Cancer Symptom Scale and EQ-5D) will be performed prior to treatment. Assessments will be performed at each cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period.
Health Resource Utilization		X	Except Cycle 1. Note that concomitant medication collection will be included.

Table 5.1-3: On-Treatment Assessments for Subjects Randomized to Arm B, Chemotherapy (CA209331)

Procedure	Cycle 1 Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) (C1D1)	Cycle 2 to x Day 1 of a 21-day Cycle (Every 3 Weeks ± 3 Days) C2D1 to CxD1	Notes
Study Drug			
Administer Study Drug	X (See Note)	X (See Note)	Topotecan: 1.5 mg/m^2 administered as 30-minute IV infusion or 2.3 mg/m^2 oral capsule (round dose to nearest 0.25 mg) once daily on Days 1 to 5 of a 21-day cycle. Amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC treatment): 40 mg/m² administered as 5-minute IV infusion once daily on Days 1 to 3 of a 21-day cycle. IVRS should be called within 1 day prior to study drug administration to receive vial assignment. Note: Treatment should begin within 3 business days of randomization. Subjects assigned to topotecan may be dosed no less than 14 days between doses and no more than 3 days from the scheduled dose. Subjects assigned to amrubicin may be dosed no less than 16 days between doses and no more than 3 days from the scheduled dose.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, Cl = chloride, CNS = central nervous system, CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, HR = heart rate, IVRS = interactive voice response system, K = potassium, LDH = lactate dehydrogenase, LFT = liver function tests, Mg = magnesium, MRI = magnetic resonance imaging, Na = sodium, NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events, O2 = oxygen, P = phosphorus, SAE = serious adverse event, T.Bili = total bilirubin, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine, WOCBP = women of childbearing potential

Table 5.1-4: Follow-Up Assessments for All Treatment Groups (CA209331)			
Procedure	**X, Follow-Up Visits 1 and 2[a]**	**S, Survival Follow-Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	Non-SAEs and SAEs must be collected up to 100 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected. SAEs should be approved in Trial Access Online (TAO) within 5 days from entry.
Review concomitant medications	X		This includes subsequent cancer therapy and concomitant medication taken up to 100 days after study drug discontinuation
Laboratory Tests	X		CBC with differential, uric acid, BUN, serum creatinine, Na, K, Ca, Mg, Cl, P, bicarbonate (optional), glucose, AST, ALT, t.bili, ALP, LDH.
Thyroid Function Testing	X		TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X		Serum or urine
ECG, Echocardiogram (LVEF) or MUGA	X		Only at Follow-up Visit 1
Efficacy Assessments			
Radiographic Tumor Assessment	See Note	See note	See Table 5.4-1 for schedule of CT/MRI assessments. For subjects without previous disease progression only.
Exploratory Biomarker Assessments			
Biomarker samples ([redacted], whole	See Note	See note	Collection of Biomarker samples at time of

Table 5.1-4: Follow-Up Assessments for All Treatment Groups (CA209331)			
Procedure	**X, Follow-Up Visits 1 and 2[a]**	**S, Survival Follow-Up Visits[b]**	**Notes**
blood, tumor biopsy)			progression is optional. See Table 5.6-1or Table 5.6-2 of Biomarker Sampling Schedule.
Outcomes Research Assessments			
Patient Reported Outcomes (PRO)	X	EQ-5D only	Both the Lung Cancer Symptom Scale and EQ-5D will be given in Follow-up Visits 1 & 2. In Survival Visits, EQ-5D is collected every 3 months for the first year of the Follow-up Phase, then every 6 months thereafter.
Subject Status			
Survival Status	X	X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information and assess subsequent anti-cancer therapy.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, Cl = chloride, CT = computed tomography, ECG = electrocardiogram, IVRS = interactive voice response system, K = potassium, LDH = lactate dehydrogenase, Mg = magnesium, MRI = magnetic resonance imaging, Na = sodium, NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events, O2 = oxygen, P = phosphorus, SAE = serious adverse event, T.Bili = total bilirubin, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine, WOCBP = women of childbearing potential

[a] Follow-up visits occur as follows: X01 = 35 days (± 7 days) from last dose, X02 = 80 days (± 7 days) from X01

[b] S, Survival visits continue every 3 months (± 7 days) after Follow-up Visit 2 until death, lost to follow-up, or withdrawal of study consent

5.1.1 Retesting During Screening

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

5.2 Study Materials

The following materials will be provided to the site by BMS.

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Serious Adverse Events (or eSAE) case report forms
- Lung Cancer Symptom Score and EuroQol Group's EQ-5D questionnaires
- RECIST 1.1 pocket guide.

5.3 Safety Assessments

Safety assessments include AEs, physical examinations, vital signs, ECOG performance status, assessment of signs and symptoms, laboratory tests, pregnancy tests as outlined in Section 5.1. Some of the assessments outlined in Section 5.1 may not be captured as data in 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

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

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days of randomization.

Contrast-enhanced computed tomography (CT) of the chest and CT or magnetic resonance imaging (MRI) of abdomen and any other known sites of disease are the preferred methods of radiographic assessment of tumors. Imaging of the pelvis is required at screening; subsequent scans of the pelvis are required for subjects with lesions present at baseline, or as clinically indicated. Brain MRI scan is the preferred imaging method for evaluating CNS metastasis, and

assessment is required at screening. Subjects with incidental brain metastases findings at screening will need to undergo radiation treatment first to be eligible. 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.

All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. 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 are not adequate for assessment of RECIST 1.1 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 is identified in target disease or when progression in bone is suspected.

Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 6 weeks, or sooner if clinically indicated.

Subjects will be evaluated for tumor response beginning 6 weeks from the date of first dose (± 5 days), then every 6 weeks (± 5 days) thereafter up to 30 weeks, then it will be every 12 weeks (± 5 days) until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends. See Table 5.4-1 for a schedule of tumor assessments. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST 1.1 criteria; see Appendix 2.

Table 5.4-1: Schedule of CT/MRI Tumor Assessments(CA209331)

Time On Study	Assessment Frequency	Assessment Week (Day 1 of Week Shown)	Assessment Window
Baseline		Week 0	– 28 days
Between Week 6 and Week 30	Every 6 weeks	6, 12, 18, 24, 30	± 5 days
Beyond Week 30	Every 12 weeks	42, 54, 66+	± 5 days

Note: Tumor assessments will continue until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends.

5.4.1 Primary Efficacy Assessment

The primary endpoint is OS in all randomized subjects. See Section 8.3.1 for the definition of OS. Every effort will be made to collect survival data on all subjects including subjects

withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. 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 Assessment

Key secondary endpoints include PFS and ORR, based on investigator assessment using RECIST 1.1 criteria.

Subjects achieving a timepoint response of CR or PR will require confirmation for BOR determination as per RECIST 1.1, according to the protocol defined tumor assessment schedule. 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 (± 5 days).

The investigator assessed ORR will be further characterized by the investigator-determined DOR and time to response (TTR).

See Section 8.3.2 for further details.

5.5 Pharmacokinetic and Immunogenicity Assessments

PK and immunogenicity samples will be collected according to the schedule listed in Table 5.5-1 for all subjects treated with nivolumab and analyzed by validated assays.

All on-treatment PK timepoints are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Separate, detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and immunogenicity samples will be provided in the central lab manual.

Table 5.5-1: Pharmacokinetics and Immunogenicity Sampling Schedule (Nivolumab) (CA209331)

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1	predose[a]	00:00	X	X
Cycle 3 Day 1	predose[a]	00:00	X	X
Cycle 11 Day 1	predose[a]	00:00	X	X
Cycle 19 Day 1	predose[a]	00:00	X	X
Cycle 27 Day 1	predose[a]	00:00	X	X
Cycle 39 Day 1	predose[a]	00:00	X	X
Day 1 of every 12th cycle from Cycle 39 until discontinuation of study drug or maximum up to 2 years of treatment	predose[a]	00:00	X	X

PK - pharmacokinetics

[a] Predose (0 Hour) samples may be collected up to 4 days prior to dosing. However, if a predose sample is collected, and the dose is subsequently delayed, an additional predose sample should not be collected.

5.6 Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab will be investigated in tumor specimens obtained at screening, and in peripheral blood taken both at screening (prior to first dose of study drug) and during the study, from all randomized subjects as outlined in Table 5.6-1 and Table 5.6-2. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual.

Table 5.6-1: Biomarker Sampling Schedule for Subjects Randomized to Nivolumab (CA209331)

Collection Timing[a]	[redacted]	Tumor	Whole Blood
Study Day		Tumor Biopsy[c]	SNP
Screening		X[d]	
C1D1			X
C1D8[e]			
C2D1			
C4D1			
Upon Progression[f]		X	

[a] Biomarker sampling occurs prior to dosing and can occur ± 3 days from the scheduled time.

[redacted]

[c] Optional biopsies upon progression may be taken at the discretion of the investigator

[d] Submission of a tumor sample prior to randomization is mandatory.

[e] Samples on non-study drug dosing days are optional.

[f] Samples from subjects who have confirmed progression are optional. For subjects being treated beyond progression (per Section 4.5.4), samples should be collected at the time of confirmed progression, requiring discontinuation of study therapy

Table 5.6-2:	**Biomarker Sampling Schedule for Subjects Randomized to Chemotherapy (CA209331)**	
Collection Timing[a]	**Tumor**	**Whole Blood**
Study Day	Tumor Biopsy[c]	SNP
Screening	X[d]	
C1D1		X
C1D15[e]		
C2D1		
C3D1		
Upon Progression[f]	X	

[a] Biomarker sampling occurs prior to dosing and can occur ± 3 days from the scheduled time.

[redacted]

[c] Optional biopsies on-treatment and upon progression and may be taken at the discretion of the investigator.

[d] Submission of a tumor sample prior to randomization is mandatory.

[e] Samples on non-study drug dosing days are optional.

[f] Samples from subjects who have confirmed progression are optional.

5.6.1 Tumor Tissue Specimens

Archival or recently collected FFPE tumor tissue collected prior to enrollment must be sent at screening to a central laboratory for retrospective determination of PD-L1 status using an analytically verified IHC assay.

A biopsy sample of subjects who experience progression at any time while on treatment is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy.

Biopsy samples may be used for the following assessments. Tumor tissue collection details are provided in Section 5.6.1.3.

[redacted]

5.6.1.2 DNA and RNA Genomic Assessment

DNA or RNA extracted from tumor provided may be subject to whole genome or exome sequencing using next-generation sequencing to identify mutational load and transcriptional expression.

5.6.1.3 Tumor Sample Collection Details

Archival tumor specimens are acceptable. For subjects without available/acceptable archival tissue, new biopsies must be obtained.

Biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates are not acceptable. Tumor samples obtained from bone metastases are not acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step.

Formalin-fixed paraffin embedded tissue may be evaluated also by fluorescence in situ hybridization (FISH), genetic mutation detection methods, and/or by quantitative polymerase chain reaction (QPCR) for exploratory analyses of prognostic or predictive molecular markers associated with SCLC (eg, gene mutation, amplification or overexpression), to determine if these factors influence response to nivolumab. Such analyses will be completed retrospectively and within the scope of informed consent.

If feasible, tumor biopsies may be obtained for subjects who have progressed on nivolumab treatment. Changes in expression of immunoregulatory proteins will be assessed in these specimens.

If a new biopsy is taken, up to 4 core biopsies are recommended. An assessment of biopsy quality by a pathologist is encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided equally into FFPE samples and RNAlater.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

Pathology report should be provided with tumor samples.

5.6.2 Peripheral Blood Markers

5.6.2.1 Single Nucleotide Polymorphisms (SNPs)

Whole blood will be collected from all subjects prior to treatment to generate genomic DNA for Single Nucleotide Polymorphism (SNP) analyses and serve as a reference for tumor mutational profiling, unless restricted by local regulations. [redacted]

5.7 Outcomes Research Assessments

The evaluation of health related quality of life is an increasingly important aspect of a clinical efficacy. Such data provides an understanding of the impact of treatment from the subjects' perspective and offers insights into the patient experience that may not be captured through physician reporting.

The LCSS will be collected to assess the impact of study treatment on patient reported disease related symptoms. The LCSS is a validated instrument designed to assess the impact of treatment on disease-related symptoms. It consists of 6 symptom specific questions related to dyspnea, cough, fatigue, pain, hemoptysis and anorexia plus 3 summary items: symptom distress, interference with activity, and global health related quality of life (HRQoL). The degree of impairment is recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score.[24,25,26]

The EQ-5D will also be collected in order to assess the impact of study treatment on generic health related quality of life, which will also be used in populating health economic models most notably, cost effectiveness analysis. The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.[27]

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, etc) will be collected for all randomized subjects. Specifically, healthcare resource utilization is evaluated based on the number of medical care encounters such as hospital admissions and their

duration, outpatient visits, diagnostic tests and procedures, concomitant medications and reasons for the encounters.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Serum samples collected at timepoints identified in Table 5.5-1 will be analyzed by a validated immunogenicity assay. As part of the immunogenicity assessment, samples may also be analyzed for neutralizing antibodies by a validated method. All on-treatment immunogenicity timepoints are intended to align with days on which nivolumab is administered. If a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab antibodies for technology exploration purposes.

In addition, serum samples designated for PK [redacted] assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

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 causal 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.)

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity.

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

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 (eg, 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 drug (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 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. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). Subjects, who are randomized but never treated with study drug, must have SAEs collected for 30 days from the date of randomization.

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 CRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the electronic CRF 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).

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

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 exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in 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

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 of awareness of the event 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 when all three of the following are present:

1) Aminotransaminase (AT, ALT or AST) elevation > 3 times upper limit of normal (ULN)
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
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.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

One independent committee will be utilized, a DMC. The DMC will be utilized to provide general oversight and safety considerations for this study, CA209331. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study.

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

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

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

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

In this study, the primary endpoint of OS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided). Approximately 560 subjects will be randomized at a ratio of 1:1 into two arms: Arm A (nivolumab); Arm B (chemotherapy: topotecan or amrubicin). For sample size calculation, non-proportional hazard model with a piecewise exponential distributions in both arms are assumed. Based on published survival curves for topotecan, a 2-piece exponential distribution with an 8-month median OS and taking into account that a limited number of subjects might receive immuno-oncology as subsequent therapy, a conservative 5% 2-year survival rate is assumed for the control arm. A delayed effect for nivolumab with a hazard ratio (HR) of 1 for the first 8 months and an HR of 0.5 thereafter is assumed The final analysis will take place 34 months after the first patient have been randomized and no formal interim analysis will be conducted. The 560 subjects are expected to be randomized in 18 months, resulting in about 16 months of follow-up for the last subject randomized at the time of the primary analysis. It is anticipated that approximately 480 events will be observed at the time of the analysis, leading to 90% power to detect a difference in overall survival as tested via a log-rank test with a two-sided 0.05 type I error rate. Power calculations were performed using EAST® Software (version 6.4.1).

The decision to incorporate the China subset into the overall population for analysis is the result of a review of the protocol statistical assumptions in comparison to recent data from the CA209032 study in 2L+ SCLC subjects.[28] The data from CA209032, which were not available at the time of protocol design, suggest a delayed effect of nivolumab with a non-proportional hazard for survival. Additionally, review of recently generated real-world data for topotecan resulted in updated assumptions for the control arm. Given the updated statistical assumptions, incorporation of the China subset into the study analyses grants adequate statistical power by increasing the study sample size.

Table 8.1-1: Sample Size Justification

Primary Endpoint	**OS**
Power	90%
Alpha level	0.05
Sample size	560
Accrual duration	18 months
Timing of the analysis from randomization of first subject (months)	34
Hypothesized OS rate at 8 months	50% in both arms (HR=1 up to Month 8)
Hypothesized OS rate at 24 months	5% vs 16% (HR=0.5 from Month 8)
Expected Average HR	~0.745
Expected number of event at 34 months	482

8.2 Populations for Analyses

- All enrolled subjects: All subjects who sign an informed consent form and are registered into the IVRS
- All randomized subjects: All enrolled subjects who are randomized to any treatment arm in the study. This is the primary dataset for analyses of efficacy and baseline characteristics.
- All treated subjects: All enrolled subjects who received at least one dose of nivolumab, or chemotherapy. This is the primary dataset for dosing and safety.
- PK subjects: All enrolled subjects with available serum time-concentration data from randomized subjects dosed with nivolumab.
- All PD-L1 tested subjects: All subjects, randomized or not, who had a tumor biopsy specimen available for PD-L1 expression testing (validated assay). This includes both randomized and screen failure subjects.
- All randomized subjects with quantifiable PD-L1 expression at baseline: Randomized subjects with at least one tumor sample collected at baseline, with number viable tumor cells ≥ 100, and percentage of viable tumor cells exhibiting PD-L1 membrane staining ≥ 0%.
- Tumor Mutational Burden (TMB) evaluable Subjects: All randomized subjects with baseline evaluable TMB

- Biomarker subjects: All treated subjects with biomarker data available.
- China Population: all subjects enrolled in China. Additional analyses exploring the consistency of findings in the China cohort may be conducted. Details of these analyses will be provided in the analysis plan.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

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 subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

8.3.2 Secondary Endpoint(s)

Secondary endpoints include ORR and PFS.

8.3.2.1 Progression Free Survival

PFS is defined as the time from randomization to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress 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 on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. Tumor response will be assessed every 6 weeks (± 5 days) (from the first dose of study drug) until Week 30, and every 12 weeks (± 5 days). Tumor assessment will continue until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond progression), lost to follow-up, withdrawal of study consent, or the study ends.

8.3.2.2 Objective Response Rate

The ORR will be based on the best overall response on study defined using RECIST 1.1, as assessed by the investigator. ORR is defined as the proportion of all randomized subjects whose BOR from baseline is either a CR or PR per RECIST 1.1 criteria. BOR is determined by the best response between the date of randomization and the date of objectively documented progression or the date of subsequent anti-cancer therapy, 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 tumor assessments before initial RECIST 1.1 defined progression. The comparison of ORR will be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors as described in Section 3.1 associated odds ratio and 95% CI will be calculated. Rates and their 2-sided exact CI will be calculated by the method of Clopper and Pearson for each randomized arm.

In addition, DOR and TTR will be summarized in each randomized arm. DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTR is defined as the time from randomization to the date of the first confirmed CR or PR. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

8.3.3 Exploratory Endpoint(s)

PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an IHC assay.

Saf**ety and tolerability objective** will be measured by the incidence of AEs, serious adverse events, deaths, and laboratory abnormalities.

Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

Tumor Mutational Burden (TMB) is measured using FoundationOne CDxTM (F1CDx) assay, a comprehensive genomic profile (CGP) assay based on baseline tumor tissue. TMB is defined as the number of somatic, coding, base substitution, and indel mutations per megabase of genome examined. All base substitutions and indels present at 5% allele frequency or greater in the coding region of targeted genes, including synonymous alterations, are initially counted before filtering as described below. Synonymous mutations are counted in order to reduce sampling noise. While synonymous mutations are not likely to be directly involved in creating immunogenicity, their presence is a signal of mutational processes that will also have resulted in nonsynonymous mutations and neoantigens elsewhere in the genome. Non-coding alterations were not counted. Alterations listed as known somatic alterations in COSMIC and truncations in tumor suppressor genes were not counted, since our assay genes are biased toward genes with functional mutations in cancer.

Alterations predicted to be germline by the somatic-germline-zygosity algorithm were not counted. Alterations that were recurrently predicted to be germline in our cohort of clinical specimens were not counted. Known germline alterations in dbSNP were not counted. Germline alterations occurring with two or more counts in the ExAC database were not counted.

To calculate the TMB per megabase, the total number of mutations counted is divided by the size of the coding region of the targeted territory.

Definition of high tumor mutational burden: high TMB will be provided in Statistical Analysis Plan.

Time to Symptom deterioration (TTSD) is defined as the time between the date of randomization and the first date of a 10 point or more increase from baseline in the LCSS Average Symptom Burden Index (ABSI). Subjects who did not meet the criteria of a 10 points or more increase from baseline in LCSS ASBI will be censored on their last LCSS assessment date. Subjects who did not have any on study LCSS assessment will be censored on their date of randomization.

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.

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 ABSI score at any time between randomization and Week 12/Week 24, respectively.

Subjects' overall health status will be assessed using The EuroQol Group's self-reported health status measure (**EQ-5D**). EQ-5D essentially has 2 health status components - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ Vas records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).[29]

Serum concentrations will be used to characterize the PK of nivolumab using a population PK approach and to explore exposure-safety and exposure-efficacy relationships.

Other exploratory endpoints for phamacogenomics, immunogenicity and outcomes research are discussed in detail in Sections 8.4.5 through 8.4.7.

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

All hypothesis testing will be two-sided based on a significance level of 0.05 except for OS. If superiority of OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1) PFS
2) ORR.

The formal statistical testing for PFS will take place only if OS is statistically significant and the statistical testing for ORR will take place only if both OS and PFS are statistically significant.

8.4.2.1 Methods of Primary Endpoint

The distribution of OS will be compared in two randomized arms via a two-sided, log-rank test stratified by the stratification factors as described in Section 3.1. 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 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 (using a log-log transformation). Survival rates at 6, 12, 18, 24, 36, 48 months and 5 years will be estimated using KM estimates on the OS curve for each randomized arm provided minimum follow-up is longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula.

8.4.2.2 Methods for Secondary Endpoint

The distribution of PFS will be compared in two randomized arms using a two-sided, log-rank test stratified by the stratification factors as described in Section 3.1. 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 (using a log-log transformation).

ORR in two randomized arms will be compared using a two-sided CMH test, stratified by the same factors. An associated odds ratio and 95% CI will also be calculated. Rates and their corresponding 95% exact CI will be calculated by Clopper-Pearson method for each randomized arm.

The estimation of DOR and TTR in two randomized arms will be computed for subjects who achieve PR or CR using KM product-limit method. Median values of duration and time-to, along with two-sided 95% CI, will be calculated.

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment arm. All on-treatment AEs, drug-related AEs, late-emergent drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE version 4.0 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 v 4.0 criteria.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. This model may 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 may be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

8.4.5 Biomarker Analyses

8.4.5.1 Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum obtained from subjects on each treatment arm, summary statistics for biomarkers of [redacted] and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit. In addition, the time course of biomarker outcomes will be investigated graphically. If there is indication of a meaningful pattern across time, further analysis may be completed to characterize the relationship. Possible associations between changes in biomarker measures of interest and exposure to study drug will be explored graphic.

8.4.5.2 Pharmacogenomic Analyses

Pharmacogenomic and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to nivolumab and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily--as outlined in the exploratory objectives--on SNPs in select genes associated with immunity or on the expression of [redacted], PD-L1, [redacted] proteins in tumor specimens. Similar analyses will be completed with data regarding [redacted] and putative additional analyses to be completed using FFPE tissue.

Associations between biomarkers and efficacy measures will be analyzed on all randomized subjects with available biomarker data. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg, response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

8.4.6 Outcomes Research Analyses

LCSS questionnaire complete rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment or in follow-up), will be calculated and summarized at each assessment point.

Baseline and change from baseline of the average symptom burden index score at each assessment point will be summarized using descriptive statistics.

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem.

Summary statistics will be calculated for the population preference-based health state utility score (EQ-5D Index).

8.4.7 Other Analyses

Methodology for exploratory analyses including immunogenicity, other HRQoL assessments (PRO), and healthcare resource utilization is described in the statistical analysis plan.

8.5 Interim Analyses

No formal analysis for OS will be performed for this study.

A DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. No formal test will be performed and the study will not stop for superiority. Details will be included in the DMC charter.

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

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by 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), AE 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. 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 (eg, 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.

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 as appropriate based on 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
Complete Abstinence	If one form of contraception is required, 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. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but 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. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but 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

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
BOR	best overall response
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca	calcium
CAV	cyclophosphamide, doxorubicin, vincristine
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTA	clinical trial agreement
DILI	drug-induced liver disease
DMC	data monitoring committee
DOR	duration of objective response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ED-SCLC	Extensive Stage Disease
eg	exempli gratia (for example)

Term	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HR	hazard ratio
HRQoL	health related quality of life
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
ITIM	immunoreceptor tyrosine inhibitory motif
ITSM	immunoreceptro tyrosine-based switch motif
IU	International Unit
IUD	intrauterine device
IV	Intravenous(ly)
IVRS	interactive voice response system
K	potassium
KM	Kaplan-Meier

Term	Definition
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
LD-SCLC	Limited Stage Disease
LVEF	Left ventricular ejection fraction
mAbs	monoclonal antibodies
MRI	magnetic resonance imaging
N	number of subjects or observations
Na	sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NIMP	non-investigational medicinal products
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	Programmed death receptor-1
PFS	progression free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
Pop PK	Population PK
PR	partial response
Q2W	every 2 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCLC	small-cell lung cancer
SD	stable disease
SNP	single nucleotide polymorphism

Term	Definition
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TMB	Tumor mutational burden
TTR	time to response
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WOCBP	women of childbearing potential

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APPENDIX 1 MANAGEMENT ALGORITHMS

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

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

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

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

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

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.

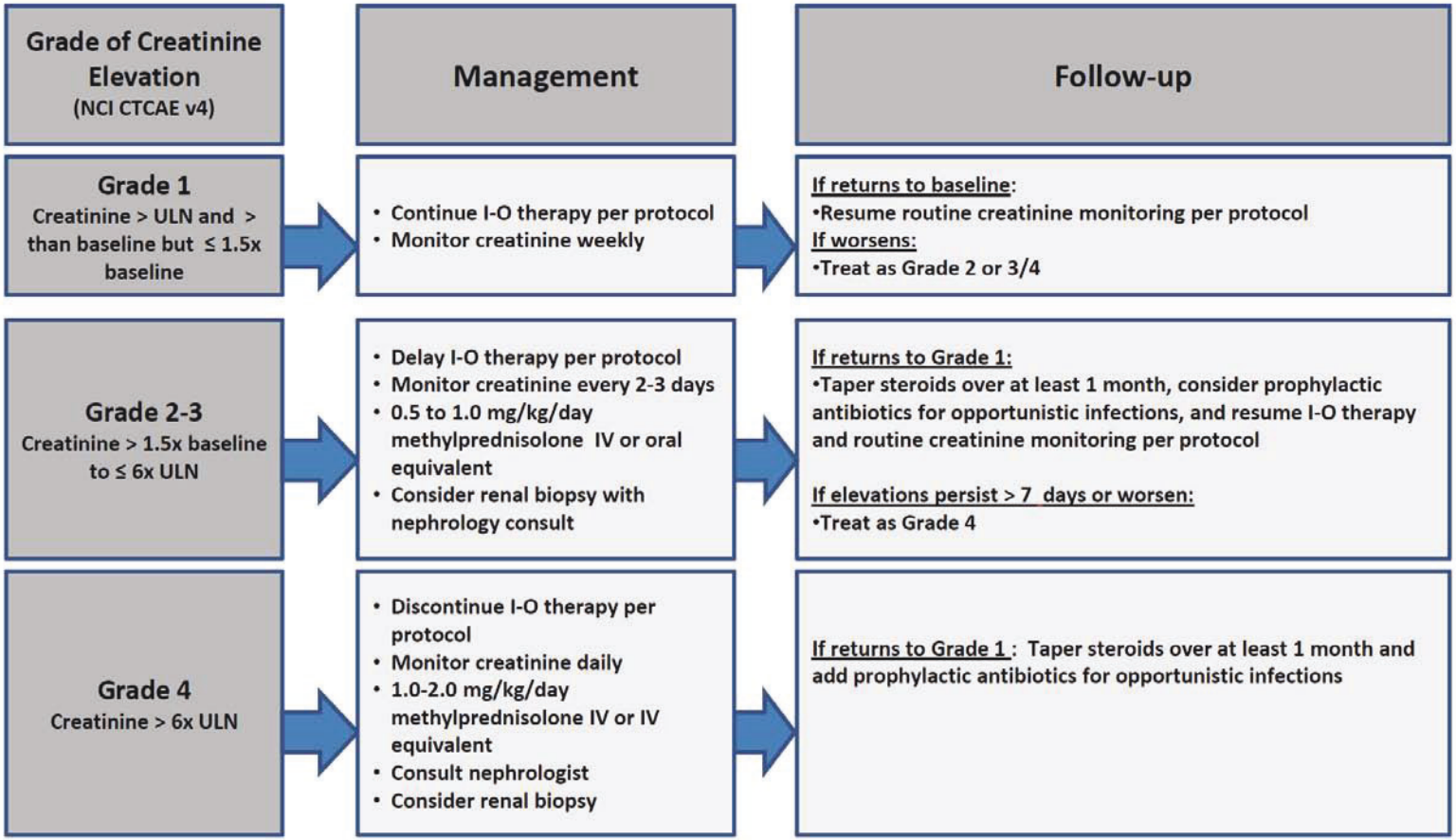
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

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

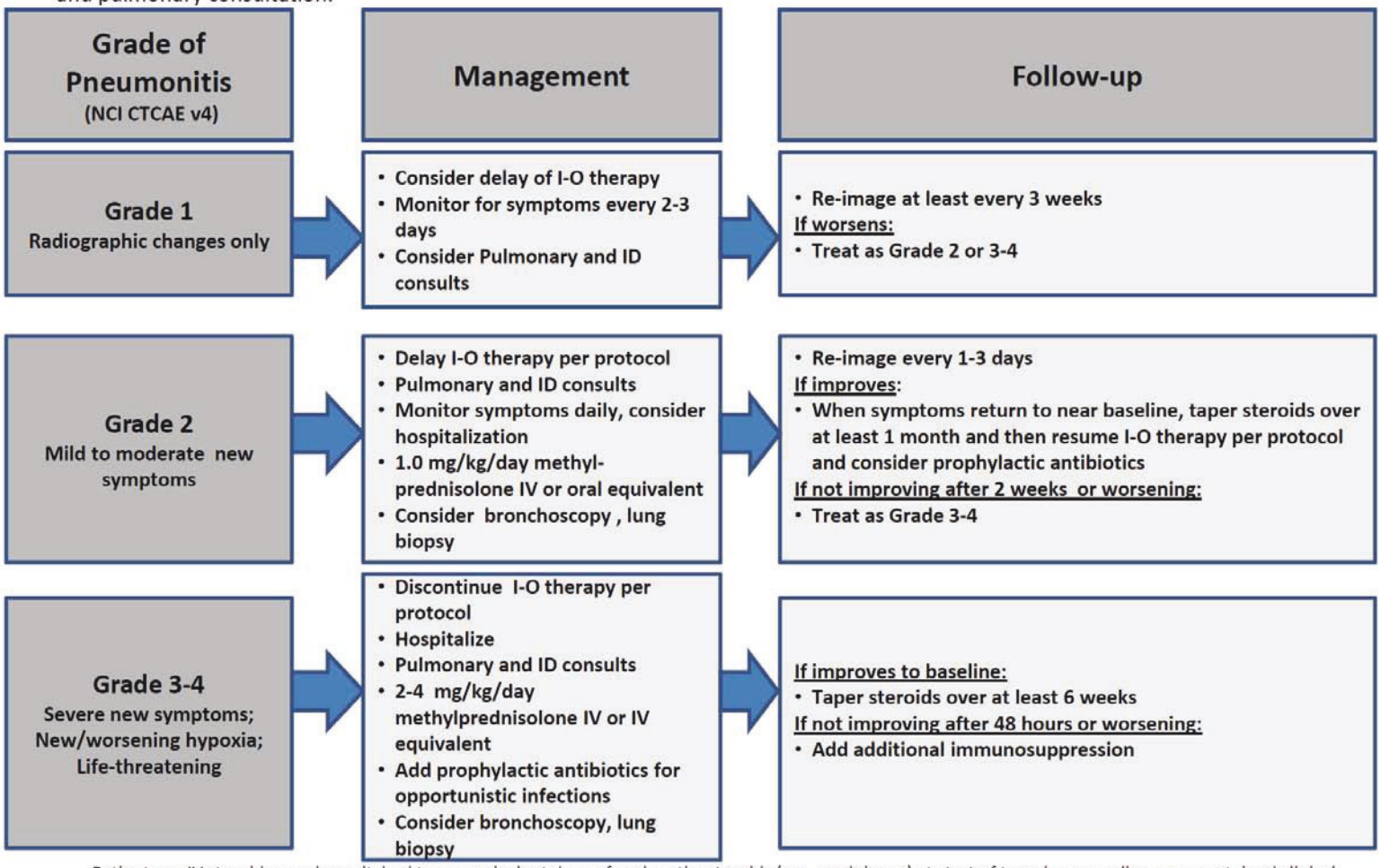


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

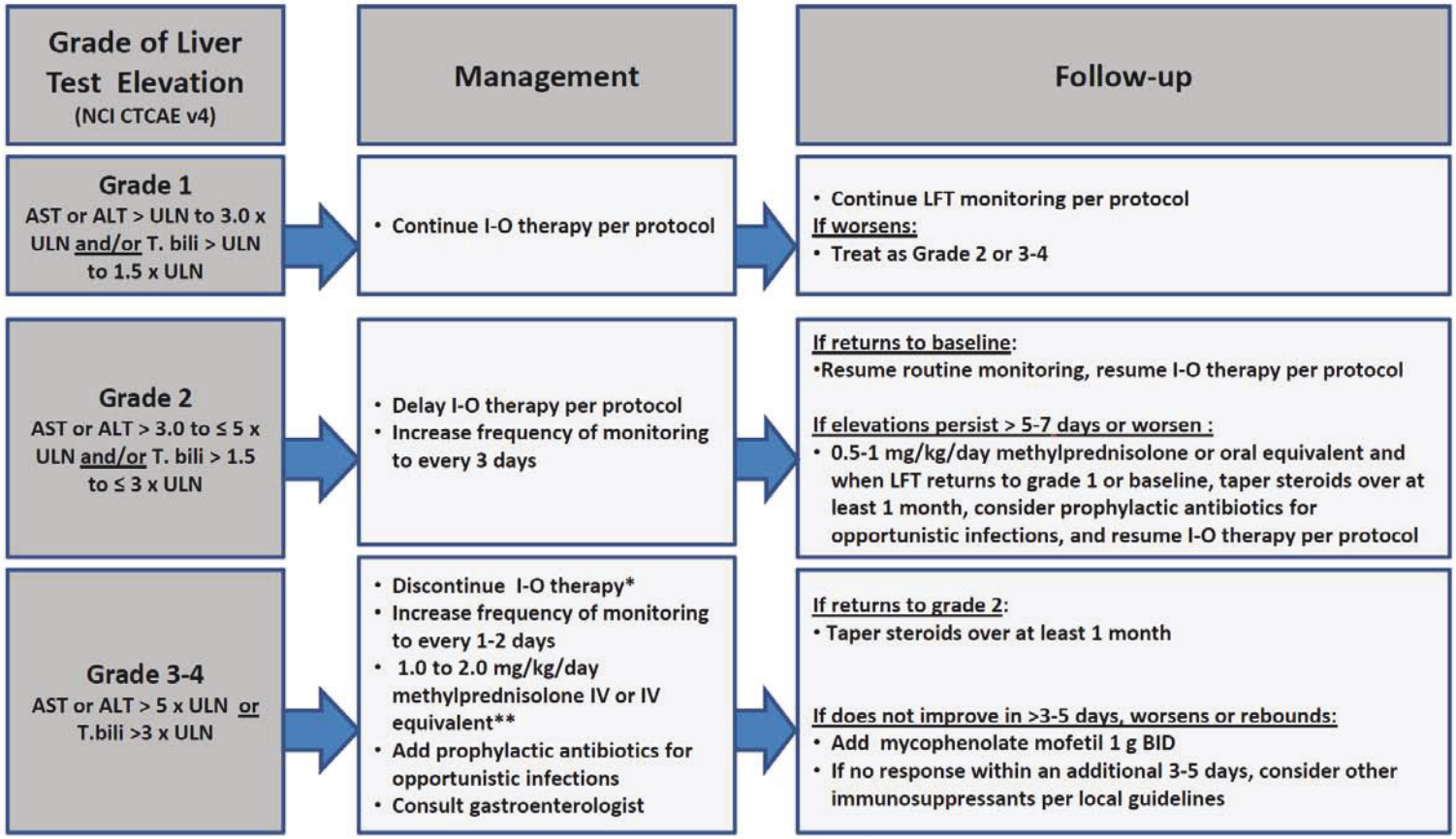


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

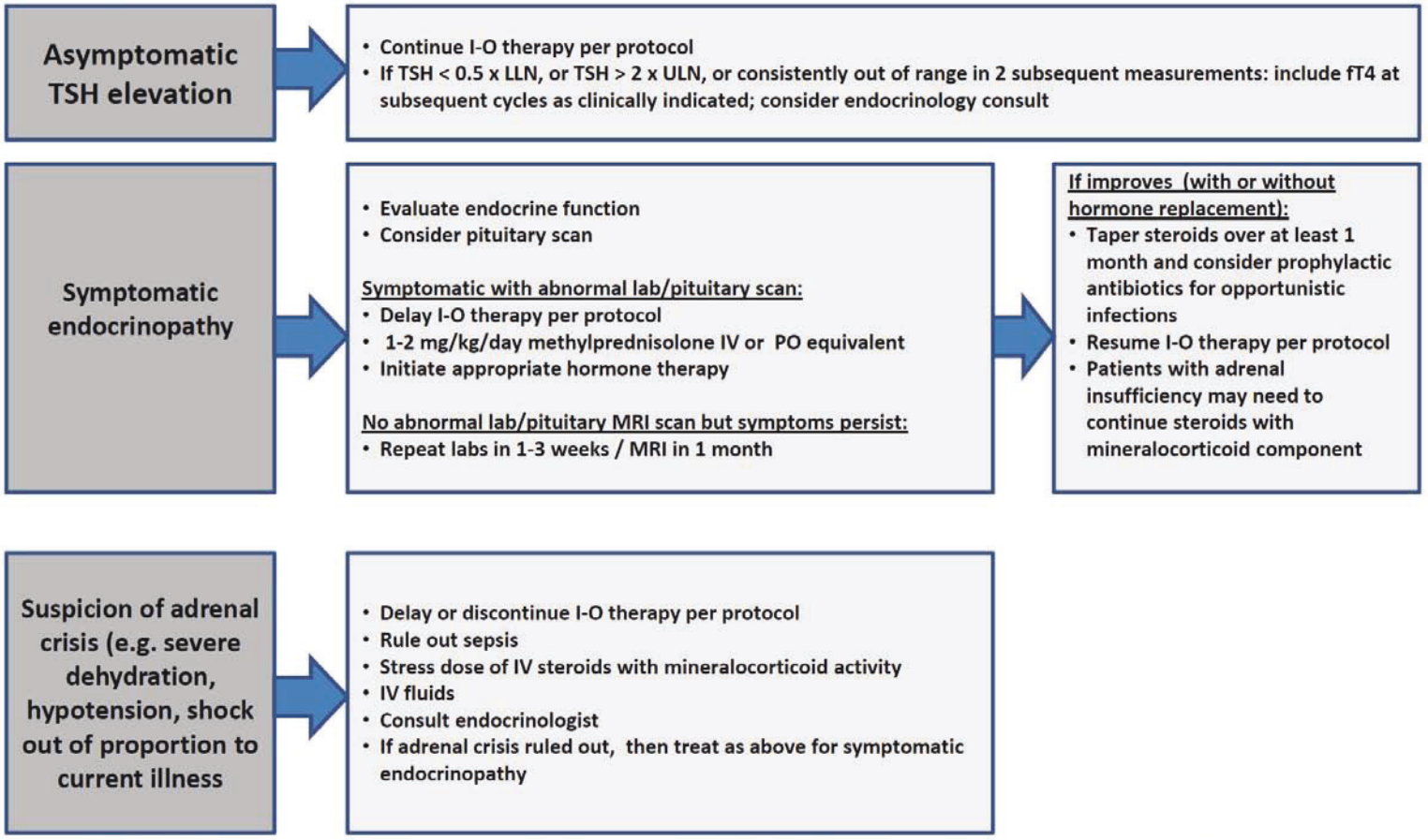
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**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.

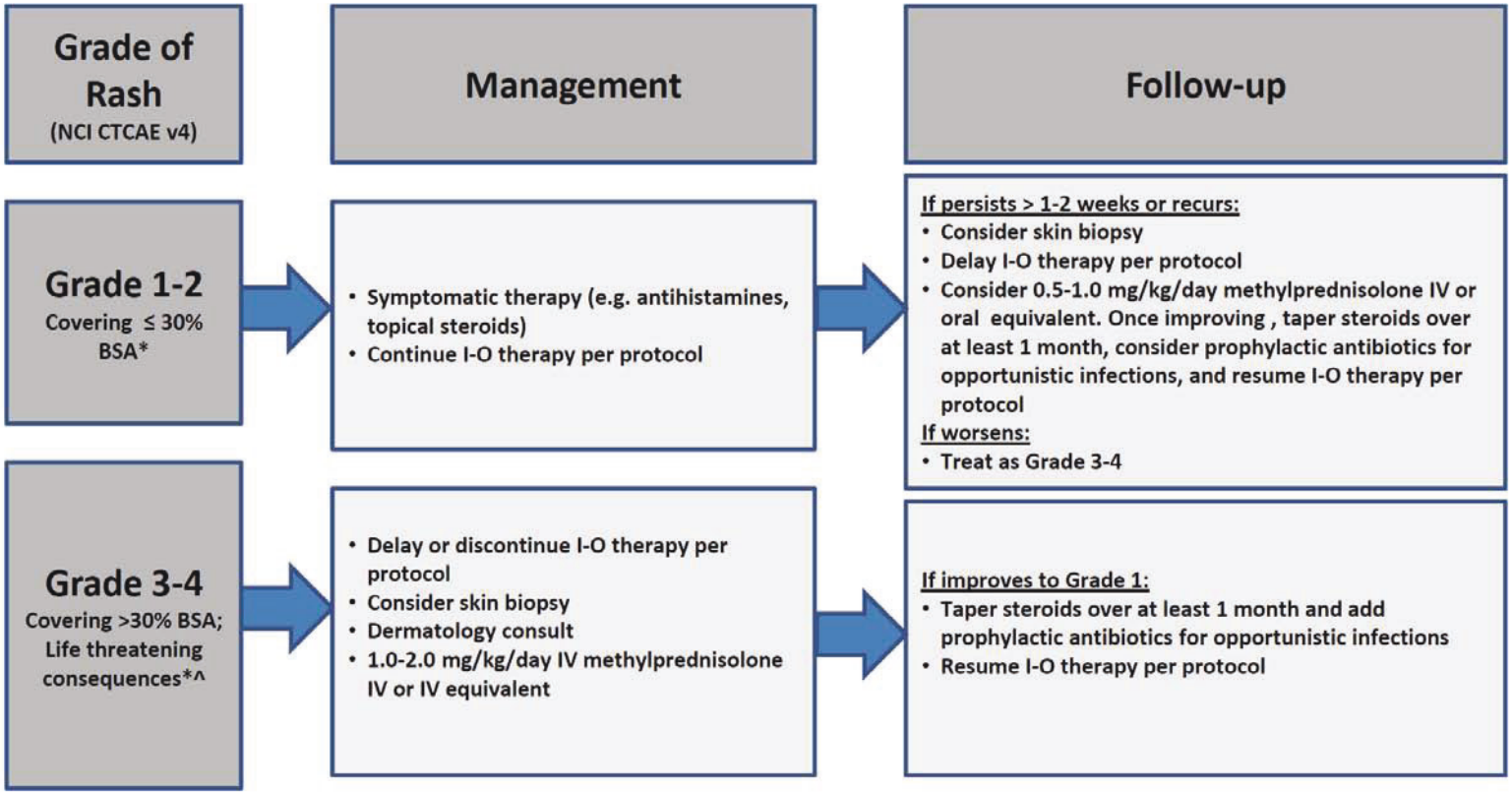


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

APPENDIX 2 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 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). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI Scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor Markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

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 below, 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.

2.1.1 Lymph Nodes

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. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target Lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

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 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. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions that Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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: in case of a lymph node believed to be present and 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).

3.1.1.3 Target 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.
- 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

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 (< 10 mm 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* 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 Non-target Lesions

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

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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: i.e. 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 subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 subject'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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject'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.*

3.3.1 FDG-PET Evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment 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:

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

4 RESPONSE CRITERIA

4.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Time Point Response: Subjects 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

Table 1:	Time Point Response: Subjects with Target (± Non-target) Disease		
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
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, NE =not evaluable

4.1.1 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation Scans

Verification of Response: Confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response are first met).

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 not to have progressive disease per RECIST 1.1.

4.2 Best Overall Response: All Timepoints

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 subject'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.

Best response is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR).

When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered not evaluable.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 - 8 weeks) that is defined in the study protocol.

Table 2: Best Overall Response when Confirmation of CR and PR IS Required

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject 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.

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).