Official Title of Study:

A Phase IIIb/IV Safety Trial of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed During or After Receiving At Least One Prior Systemic Regimen

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Clinical Protocol CA209153

A Phase IIIb/IV Safety Trial of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed During or After Receiving At Least One Prior Systemic Regimen

CheckMate 153: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 153

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Contains Global Amendment 06 and Administrative Letter 02

Study Director/ Medical Monitor

[redacted]

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

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648

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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 04	01-Dec-2017	• After 24 months from first dose, the frequency of radiographic tumor assessments will be extended from every 8 weeks to every 12 weeks. • After 24 months of treatment, the frequency of surveillance brain MRI or CT scans will be extended from every 12 weeks to every 6 months or earlier, if clinically indicated, for subjects with known brain metastases. • In Section 3.3.1, updated contraception information, required durations, references to Appendix 03, and removed redundant contraception information from Section 3.3.1 as it is included in Appendix 03. • Added Appendix 03 to show contraception information for both male and female subjects and the length of required contraception durations. • Added information for botanical treatments and adrenal insufficiency. • Updated Nivolumab Dose delay criteria, Criteria to Resume Treatment, and Treatment Discontinuation. • Updated RECIST 1.1 criteria in Appendix 01. • Updated Management Algorithms in Appendix 02 • Minor editorial and grammatical corrections
Revised protocol 03	17-Dec-2014	Incorporates Amendment 04, 03, 01, and Administrative Letter 01
Global Amendment 04	17-Dec-2014	• An additional 500 subjects will be treated to continue collecting safety information and to characterize the outcome of immune-mediated side effects. Enrollment will continue in all subgroups until a total of 1280 subjects are treated. • Amendment 04 ends enrollment under Amendment 3, which allowed enrollment for specific subgroups. • [redacted] • Nivolumab will be administered to all current and newly enrolled subjects as a 30 minute infusion, including subjects enrolled under Amendment 02. • Number of subjects specified in study schematic updated on the basis of additional enrollment numbers. • Change in the frequency of TSH/thyroid function tests for subjects randomized to Cohort B. • Minor editorial or format changes made in text.
Revised protocol 02	22-Oct-2014	Incorporates Amendment 03, 01, and Administrative Letter 01
Global Amendment 03	22-Oct-2014	• The study design has been modified. Enrollment beyond 780 subjects will continue [redacted] allow for continued enrollment in two subject subgroups

Document	Date of Issue	Summary of Change
		(Subgroup 1: Subjects who have failed two or more prior therapies, performance status (PS) of 0 1, squamous histology and Subgroup 4 squamous histology only - subjects who have failed at least 2 prior therapies with PS 2). For the two subject subgroups, enrollment will continue until regulatory decisions have been made and commercial or assistance-based supply of nivolumab is available in the subject's region based on local regulations. • Archived or fresh tumor biopsy is no longer required but is highly recommended. • Specifications to EGFR and ALK mutational status testing as part of the screening and eligibility procedures have been incorporated. • Subjects who have failed eligibility to any other PD1 or PDL1 trial due to PDL1 status are excluded. • The frequency of assessments as presented in the time and events schedule for subjects enrolled in Cohort B has been clarified • Minor editorial and format changes have been incorporated.
Amendment 02 Site Specific	03-Sep-2014	[redacted]
Revised protocol 01	20-Jun-2014	Incorporates Amendment 01 and Administrative Letter 01
Global Amendment 01	20-Jun-2014	• Throughout the protocol editorial changes have been made to clarify study cohorts and study design • Clarifications to Study design schematic for study subgroup descriptions and for randomization at 1 year of treatment. • Clarification on requirement for molecular testing for eligibility inclusion criteria • Deletion of incorrect exclusion criteria [ie, subject use of strong CYP3A4 inhibitors]) • Changes to time and events schedule (Tables 5.1-1 through 5.1-3) notes in: medical history, tumor assessment, tumor tissue/ biopsy, pharmacogenetic samples, thyroid function, pregnancy test, laboratory tests, [redacted] and study drug administration.
Original Protocol	10-Dec-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209153

Protocol Title: A Phase IIIb/IV Safety Trial of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed During or After Receiving At Least One Prior Systemic Regimen CheckMate 153: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 153

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab solution for injection, 3 mg/kg, intravenous (IV) infusion over 30 minutes every 2 weeks, until disease progression, unacceptable toxicity, or withdrawal of informed consent (Cohort A) OR for 1 year (52 weeks) only, with possibility of retreatment on disease progression (Cohort B).

Study Phase: 3b/4

Research Hypothesis: High grade (CTCAE v4.0 Grade 3-5) treatment-related select adverse events occur with a low frequency in subjects with advanced or metastatic NSCLC treated with nivolumab monotherapy.

Objectives:

Primary: To estimate the incidence of high grade (CTCAE v4.0 Grade 3-4 and Grade 5) treatment related select adverse events in subjects with advanced or metastatic NSCLC who have progressed during or after at least one prior systemic therapy and are treated with nivolumab monotherapy.

Secondary: To estimate the incidence and characterize the outcome of all high grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events in subjects with advanced or metastatic NSCLC who have progressed during or after at least one prior systemic therapy and are treated with nivolumab monotherapy.

Exploratory:

- To assess safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities in all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and in Cohorts A and B
- To estimate efficacy of nivolumab by measuring OS, PFS, ORR based on investigator assessment, and DOR in all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and in Cohorts A and B (OS, PFS and DOR only)
- To explore the evolution of Patient Reported Outcomes (PRO) using the Lung Cancer Symptoms Scale (LCSS) and EQ-5D instruments in all treated subjects, by subject subgroups, and in Cohorts A and B.
- To estimate the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks as measured by LCSS
- [redacted]
- [redacted]
- [redacted]

Study Design: In this safety study of nivolumab monotherapy, subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Eligible subjects will be treated with nivolumab administered intravenously over 30 minutes at 3 mg/kg every two weeks. Each 14 day dosing period will constitute a cycle. After 1 year (52 weeks) of treatment all subjects who are still on treatment will be randomized (1:1) to one of the two cohorts, Cohort A or Cohort B.

- Cohort A: Subjects randomized to Cohort A will continue to receive treatment until disease progression, unacceptable toxicity, or withdrawal of informed consent.
- Cohort B: Subjects randomized to Cohort B will discontinue treatment at 1 year (52 weeks). After randomization, subjects will remain on the study and will follow all study assessments [redacted] Upon progression, subjects can receive retreatment. If subjects are

[redacted] Subjects who are retreated can continue to receive study drug until further progression, unacceptable toxicity, or withdrawal of informed consent.

Study treatment can continue beyond initial investigator assessed progression, as specified in criteria presented in Section 4.3.4 Treatment Beyond Disease Progression.

The study will enroll subjects into 4 subgroups as detailed in Table 3.1-1. Enrollment will open first to subgroup 1 only. A decision to open enrollment for each of the other subgroups 2-4 will be dependent upon the sponsor review of data from the ongoing Phase 2 and 3 studies for each patient population. The decision will take into account the overall risk/benefit profile for each patient population and the determination will be made whether or not to collect additional safety and efficacy data to supplement that already collected.

At the time of Protocol Amendment 01 (June 2014), all subgroups were opened.

Protocol Amendment 03 (November 2014) allowed for continued enrollment beyond 780 subjects in two of the study subgroups. However, as of Protocol Amendment 04 (December 2014), enrollment under Amendment 03 will stop, but enrollment will continue until 500 additional subjects are treated. Enrollment will continue until a total of 1280 subjects are treated.

[redacted]

Under Protocol Amendment 04, all subjects will receive nivolumab by IV infusion administered over 30 minutes, including new and existing subjects enrolled in the study and subjects enrolled under Amendment 02.

The study will close after the last enrolled subject completes 5 year follow up. The duration of the study will be 6.5 years.

Study Population: Patients with Stage 3b/4 NSCLC (squamous or non-squamous histology) who have experienced disease progression or recurrence during or after at least one systemic therapy for advanced or metastatic disease. Subjects must meet all eligibility criteria specified in Section 3.3 of the protocol.

Study Assessments: Main assessments include: Incidence, severity and outcome of select adverse events, and specific related laboratory abnormalities. Exploratory assessments include incidence and severity of all adverse events, laboratory abnormalities, efficacy measures, patient reported outcomes [redacted].

Statistical Considerations:

Sample Size: In order to further characterize the frequency and outcome of the rather infrequent treatment related select adverse of high grade (Grade 3-5), the current study will treat approximately 780 subjects with nivolumab. This sample size will allow for estimating an incidence rate of 0.5% (n=4 subjects with events) with a 95% CI (confidence interval) of (0.14%, 1.31%), or an incidence rate of 2% (n=16 subjects with events) with a 95% CI of (1.18%, 3.31%).

This study also includes a randomization step reserved to subjects who received nivolumab for 1 year (52 weeks). In MDX1106-03, 27% of NSCLC subjects (10 of 37) were still on treatment [95% CI of (12.7%, 41.3%)] at Week 48. In the present study any subjects (all subgroups included) who are still benefiting from therapy after 52 weeks (estimated to be between 99 and 322 subjects) will be randomized in order to continue treatment without any change in Cohort A, or to discontinue treatment in Cohort B, respectively.

Endpoints: The primary objective of the study will be assessed by measuring the incidence for high grade (Grade 3-4 and Grade 5) treatment related select adverse events.

The select adverse events of interest are the following: pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events.

The secondary objective of the study will be assessed by measuring the following:

- incidence for high grade (Grade 3-4 and Grade 5) select adverse events
- median time to onset, median time to resolution (Grade 3-4) of the select adverse events

- percentage of subjects who received immune modulating medication (e.g. corticoidsteroids, infliximab, cyclophophamide, IVIG, and mycophenolate mofetil) or hormone replacement therapy, the percentage of subjects who received ≥ 40 mg prednisone equivalents, total duration of all immune modulating medications given for the select event.

Analyses:

Primary Analyses: The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) treatment related select adverse events will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) treatment related select adverse events will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

Secondary Analyses: The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) select adverse events will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) select adverse events will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

Additional descriptive statistics will include median values using the Kaplan-Meier (KM) product-limit method with 95% CI using Brookmeyer and Crowley method of time to onset and time to resolution, and will be presented for all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

Management of high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events will be characterized by measuring percentage of subjects who received immune modulating medication (or hormonal replacement therapy), percentage of subjects who received ≥ 40 mg prednisone equivalents, and total duration of all immune modulating medications given for the event, in all treated subjects who have experience high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events, by tumor histology (SQ or NSQ), and also by subject subgroups, and all randomized subjects in Cohorts A and B.

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1 INTRODUCTION AND STUDY RATIONALE

Lung cancer is the leading cause of cancer and cancer-related deaths globally, accounting for 1.6 million cases and 1.4 million deaths worldwide in 2008. [1] The majority of patients (approximately 78%) are diagnosed with advanced or metastatic disease. Prognosis for these patients remains dismal, with 5-year survival rates of less than 5%. Approximately 85% of lung cancer is non-small cell lung cancer (NSCLC). Of these, approximately 80% are non squamous and 20% are squamous histology.

Despite the increased number of treatment options available for patients with non-squamous (NSQ) NSCLC, there has been little overall survival (OS) improvement from several new agents, including pemetrexed and bevacizumab.[2,3] With the development of targeted agents for patients with tumors with driver mutations in the Epithelial Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK), some improvement in progression free survival (PFS) is realized but as a consequence of acquired resistance, the improvement in overall survival (OS) is still limited. Furthermore, patients with squamous cell NSCLC have generally not benefited from the development of new agents (eg, pemetrexed and bevacizumab). Consequently, NSCLC remains a disease with high burden and unmet medical need.

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

BMS-936558 (nivolumab) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby purportedly abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[5] Nivolumab clinical activity has been observed in heavily pretreated NSCLC subjects (n=129) in the Phase 1 multidose, dose escalation study (MDX1106-03). This study showed objective response rates (ORR) of 17% across a dose range of 1, 3 and 10 mg/kg (6%, 32%, and 18% respectively).[6] In the subjects who experienced an objective response, the median duration of response was 17 months [95% CI: 9.7, NE).[7]

In general, nivolumab has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action. [5,6,7,8]

1.1 Study Rationale

Nivolumab, an anti-PD-1 monoclonal antibody, has shown anti-tumor activity in early phase clinical trials across multiple tumor types including NSCLC, renal cell carcinoma and melanoma. The registrational development path in NSCLC is in previously treated subjects with squamous (SQ) or non-squamous (NSQ) tumor histology. In a large Phase 1 study, MDX1106-03, a total of 129 NSCLC subjects were treated with nivolumab, while the registrational NSCLC studies include 500 subjects with similar disease characteristics. As the registrational activities progress, obtaining additional specific safety data will further inform the risk/benefit assessment for nivolumab. Using a single large study is warranted in order to expand the safety database and especially to improve the precision of estimated incidence of uncommon select high-grade adverse events (AEs). In addition, this study could provide important insights into the potential contribution of the underlying disease to the incidence and severity of pulmonary AEs in NSCLC subjects.

At the time of writing Version 12 of the Investigator Brochure (clinical data cut-off 18 March 2013), the overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, was based on data observed in approximately 1500 subjects.[9] In general, for monotherapy, the safety profile was similar across tumor types in completed and ongoing clinical trials with no MTD (maximum tolerated dose) reached at any dose tested up to 10 mg/kg, and no pattern in the incidence, severity, or causality of AEs to nivolumab at these dose levels. The one exception is the incidence of pulmonary inflammation, which may be numerically greater in subjects with NSCLC possibly because in some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. For example, in study MDX1106-03, in a heavily pre-treated NSCLC cohort (N=129), treatment-related CTCAE grade 3-4 pulmonary toxicity incidence was 2%; however, in study CA209-004 in advanced and metastatic melanoma subjects (N=33) there were no grade 3-4 pulmonary toxicities in a treatment arm with nivolumab following ipilimumab. At this time no other risk factor, including prior radiotherapy, presence of lung metastases or pulmonary medical history, has been identified.[9]

Nivolumab-related AEs are mostly thought to be due to the effects of inflammatory cells on specific tissues and management of these AEs may require special consideration. Among the safety events observed, a few categories were identified as likely to be due to an immune mechanism. These select AEs may require more frequent monitoring and/or unique intervention (immunosuppressants or hormonal replacement), and are addressed in a consistent and unified manner throughout the program by specifically designed safety algorithms (See Appendix 2 for Management Algorithms).

Categories of "select AEs" have been created to group together the most common and impactful preferred terms (PTs) by organ category, providing a better estimate of the frequency of similar kinds of organ-related AEs instead of using PTs only. These select adverse events are further defined as follows:

- may differ from or be more severe than AEs caused by non-immunotherapies

- may require unique (non-standard) intervention such as immunosuppressants (or hormone replacement therapy), and
- early recognition and management may mitigate severe toxicity.

The preferred terms included in the 'select AEs' category are those that are expected to be most commonly used to describe pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, and endocrinopathies. Hypersensitivity/infusion reactions are also considered a select AE category to facilitate the pooling of the most relevant preferred terms for analyses of hypersensitivity/infusion reaction events, and not because such events fit the criteria for select AEs listed above.

The frequencies of these events in study MDX1106-03 (Phase 1 study; N = 306; heavily pre-treated subjects with different tumor types) are summarized in Table 1.1-1. The treatment-related select AEs of Grade 3-4 observed to date are rather uncommon: 6% overall in study MDX1106-03, while their incidence per category varies between 0.3% and 2% (pulmonary AEs). Of note, the 10 mg/kg cohort had numerically greater frequency of such AEs compared with the other dose levels. In the NSCLC subjects treated in the study (n=129) the overall incidence of Grade 3-4 treatment-related select AEs was 5%: 0% for skin and renal AEs, and endocrinopathies; 1% gastrointestinal, hepatic, and infusion reaction AEs; and 2% for pulmonary events.[7] Most high-grade events of special interest were observed to have resolved while addressed with systemic corticosteroids and/or other immunosuppressive agents. One exception was Grade 4 pneumonitis considered to have led to death of three subjects: two of them were treated at the 1 mg/kg dose level and had NSCLC and CRC, respectively; the third subject had NSCLC and was treated at the 10 mg/kg dose level.

Specific safety algorithms have been designed for the select categories of AEs, and are implemented in a unified manner in all current studies in the nivolumab program (See Appendix 2 for Management Algorithms). These safety algorithms assist the diagnostic, the assessment of relatedness, and the management of the select AEs, also they are continuously evaluated and adjusted as experience accumulates. The current study will focus on improving precision around the frequency of high-grade select AEs, and on obtaining information on their outcome.

Table 1.1-1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in MDX1106-03

Preferred Term	0.1 mg/kg n=17		0.3 mg/kg n=18		1 mg/kg n=86		3 mg/kg n=54		10 mg/kg n=131		Total N=306	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any Select AE	**8 (47)**	**1 (5.9)**	**9 (50)**	**0**	**42 (49)**	**3 (4)**	**23 (43)**	**2 (4)**	**58 (44)**	**13 (10)**	**140 (46)**	**19 (6)**
Any Endocrinopathies	**4 (24)**	**0**	**2 (11)**	**0**	**9 (11)**	**0**	**4 (7)**	**0**	**10 (8)**	**3 (2)**	**29 (10)**	**3 (1)**
Endocrinopathies Thyroid	3 (18)	0	2 (11)	0	9 (11)	0	4 (7)	0	8 (6)	2 (2)	26 (9)	2 (1)
Blood TSH increased	2 (12)	0	1 (6)	0	2 (2)	0	2 (4)	0	4 (3)	1 (1)	11 (4)	1 (0.3)
Hypothyroidism	1 (6)	0	1 (6)	0	5 (6)	0	1 (2)	0	3 (2)	1 (1)	11 (4)	1 (0.3)
Any Skin AEs	**3 (18)**	**0**	**5 (28)**	**0**	**27 (31)**	**0**	**12 (22)**	**0**	**28 (21)**	**1 (1)**	**75 (25)**	**1 (0.3)**
Rash	3 (18)	0	3 (17)	0	20 (23)	0	5 (9)	0	14 (11)	0	45 (15)	0
Pruritus	0	0	1 (6)	0	15 (17)	0	3 (6)	0	13 (10)	1 (1)	32 (11)	1 (0.3)
Any GI AE	**1 (6)**	**0**	**2 (11)**	**0**	**19 (22)**	**0**	**7 (13)**	**0**	**14 (11)**	**3 (2)**	**43 (14)**	**3 (1)**
Diarrhea	1 (6)	0	2 (11)	0	19 (22)	0	6 (11)	0	13 (10)	3 (2)	41 (13)	3 (1)
Any hepatic AE	**0**	**0**	**2 (11)**	**0**	**8 (9)**	**0**	**3 (6)**	**2 (4)**	**5 (4)**	**2 (2)**	**18 (6)**	**4 (1)**
ALT increased	0	0	1 (6)	0	6 (7)	0	1 (2)	0	3 (2)	**1 (1)**	11 (4)	1 (0.3)
Any Pulmonary AE	1 (6)	**0**	1 (6)	**0**	**6 (7)**	**3 (4)**	**2 (4)**	**0**	**7 (5)**	**3 (2)**	**17 (6)**	**6 (2)**
Pneumonitis	1 (6)	0	0	0	4 (5)	2 (2)	1 (2)	0	6 (5)	2 (2)	12 (4)	4 (1)
Infusion reaction	**0**	**0**	**1 (6)**	**0**	**3 (4)**	**0**	**3 (6)**	**0**	**8 (6)**	**2 (2)**	**15 (5)**	**2 (1)**
Infusion-related reaction	0	0	1 (6)	0	3 (4)	0	3 (6)	0	5 (4)	0	12 (4)	0
Hypersensitivity	0	0	0	0	0	0	1 (1.9)	0	3 (2)	2 (2)	4 (1)	2 (1)

Abbreviations: ALT: alanine aminotransferase, TSH: thyroid stimulating hormone

Source: Preliminary data, MDX1106-03. Clinical data cut-off date: 18-Mar-2013

1.1.1 Rationale for Study Design

The main objective of the study is to provide additional insight into the frequency of high-grade select AEs and their outcome, and thus supplement the growing safety database of nivolumab-treated subjects. This study will treat approximately 780 subjects in order to estimate the incidence of the rare high grade (CTCAE V4 Grade 3-4 and Grade 5) treatment-related select AEs with greater precision and characterize their outcome (between 0 and 2% incidence per event type in NSCLC subjects treated with nivolumab monotherapy in previous studies).

The safety assessment for the patient subgroups 1-3 is expected to be similar and hence the size of those individual cohorts will not be fixed. There is the possibility that the safety assessment of subgroup 4 (PS2) could be different and so enrollment is limited to 100 subjects.

Also, the large number of subjects enrolled will allow an opportunity to describe, as an exploratory objective, two different treatment durations in terms of safety, efficacy, and patient-reported outcomes (PRO) data. In study MDX1106-03, after 48 weeks of treatment with nivolumab at the 3 mg/kg dose level, 27% of the NSCLC subjects were still on treatment (95% CI: 12.7%, 41.3%). Following on that observation, in the current study, subjects who are still benefiting from the drug after completing 1 year of treatment will be randomized 1:1 in two cohorts. Subjects randomized to Cohort A will continue on treatment until progression, unacceptable toxicity, or withdrawal of informed consent. Subjects randomized to Cohort B will remain on study but will discontinue treatment. Upon disease progression, subjects in Cohort B will be allowed to resume treatment. Subjects randomized to Cohort B who restart treatment will then continue on treatment until progression, unacceptable toxicity, or withdrawal of informed consent.

An additional 500 subjects will be treated under Protocol Amendment 04 (December 2014) to continue collecting safety information and to characterize the outcome of immune-mediated side effects. These additional data will provide a larger data set to inform the risk/benefit profile of the use of nivolumab in lung cancer patients and will help to further clarify the effectiveness of the current treatment algorithms for managing drug- mediated toxicities (See Appendix 2 for Management Algorithms).

1.1.2 Rationale for Subject Subgroups

Obtaining additional data on the incidence and outcome of high grade (Grade 3-4 and Grade 5) select events in a similar patient population as that included in the nivolumab registrational NSCLC studies is warranted to further support the assessment of risk/benefit.

Obtaining similar data in patient populations that have been previously excluded from the registrational studies (ie. subjects with PS 2) will provide critical information for the nivolumab clinical development program, and also for medical oncologists when making treatment decisions. Treatment with nivolumab in subjects with PS 2 is planned to allow for signal detection for both safety and efficacy as an exploratory objective (subgroup 4). This data will inform if further investigation of the risk/benefit profile of nivolumab in this subject subset is justified.

1.1.2.1 Rationale for Exploring Fixed Treatment Duration vs Continuous Treatment on Maintaining Tumor Response

In the current Phase 2/3 trials subjects are continuously treated with nivolumab on a schedule of 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity or withdrawal of informed consent. Safety and efficacy profile of nivolumab monotherapy in a schedule with defined treatment duration and retreatment upon disease progression has not been previously assessed. There is evidence for other cancer immunotherapies that administration of treatment for a fixed period of time can translate into prolonged benefit, eg, ipilimumab or aldesleukin.[10,11,12,13,14,15] In subjects with NSCLC treated in MDX1106-03, 50% of the observed responses occurred rapidly and were demonstrated at first tumor assessment (at 8 weeks). The most delayed response was observed shortly after 30 weeks.[16] After 1 year of treatment, 27% of NSCLC subjects (10 of 37 total; 5 of 18 for SQ and 5 of 19 for NSQ) treated at 3 mg/kg dose level were still on treatment. Moreover, most of them (9 of 10) continued to experience durable responses. For those patients that do progress after treatment discontinuation, will be allowed to receive retreatment until progression, unacceptable toxicity, or withdrawal of informed consent. Response to retreatment with immunotherapies such as ipilimumab has been shown.[17] Hence, the intention to obtain information on the effect of different treatment durations on maintaining the tumor response is warranted, as it may inform on the value of further testing of alternative schedules.

1.1.3 Rationale for Nivolumab Monotherapy

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen presenting cells (APC).[18] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[19,20,21,22] In particular, PD-L1 has been shown to be upregulated on several cancers types including NSCLC and, in some cases, correlated to negative prognosis.[23,24,25,26,27] PD-1/PD-L interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[28] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and antitumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models. Based on these and other preclinical data, PD-1 blockade by nivolumab has been pursued as a promising therapeutic strategy to reverse immune tolerance and enhance T-cell effector function in several tumor types including NSCLC.[9]

Substantial monotherapy clinical activity has been observed in ≥ second line NSCLC subjects treated in the ongoing Phase 1 study of nivolumab (MDX1106-03, Section 1.4.3.3). This study showed objective response rates (ORR, 19-26% for 3 and 10 mg/kg nivolumab) greater than the historical ORR for docetaxel (approximately 8-10%).[29,30,31] Median duration of response for NSCLC subjects in MDX1106-03 was more than 6 months, as compared to a median PFS for docetaxel and pemetrexed of approximately 3 months.[29,30,31] Furthermore, the adverse event

profile for nivolumab appears favorable versus docetaxel or pemetrexed, as hematologic toxicities are currently rare and the majority of non-hematologic toxicities are low grade and manageable.

1.1.4 Rationale for Nivolumab Dose and Schedule

The dose and schedule of nivolumab in this study will be 3 mg/kg every 2 weeks, based upon a 24 February 2012 analysis of safety, efficacy, and exposure-response data from the ongoing Phase 1 study, MDX1106-03. Anti-tumor activity was observed in NSCLC subjects at dose levels of 1, 3 and 10 mg/kg every 2 weeks. Anti-tumor activity appeared to approach a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of exposure-response analyses showed that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg administered every 2 weeks.

Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. While the spectrum, frequency, and severity of nivolumab -related AEs were generally similar across the dose levels tested, the 10 mg/kg dose level had numerically higher rates of Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on these observations, a dose of 3 mg/kg every 2 weeks was chosen for further studies. Further information on observed safety, efficacy and pharmacokinetic data from MDX1106-03 is reviewed in Section 1.4.3.1.

1.1.5 Rationale for Initial Tumor Assessment after 8 Weeks of Treatment

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 the Phase 1 MDX1106-03 study of nivolumab. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size appearing 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. Another hypothesis is that the kinetics of tumor growth may initially outpace anti-tumor immune activity in some individuals. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. For these reasons, the initial tumor assessment in MDX1106-03 was conducted at 8 weeks

To mitigate the risk of detecting false-progression early in the course of treatment with nivolumab, the initial tumor assessment in this study will take place after 8 weeks of treatment (± 5 days). Subsequent tumor assessments will take place regularly every 8 weeks (± 5 days) through 24 months of treatment, disease progression, lost to follow-up or withdrawal of study consent. After 24 months of treatment, tumor assessments will take place regularly every 12 weeks (±5 days) until the end of treatment or until disease progression, lost to follow-up or withdrawal of study consent.

1.1.6 Rationale for Tumor Tissue Collection

Aberrant expression of PD-L1 protein by tumor cells (retrospectively detected by IHC) has been reported in a number of human malignancies, especially in relation to poor prognosis in multiple tumor types, including squamous cell and non-squamous NSCLC.[23,24,25,26, 32 , 33 , 34] These findings may be explained by the notion that high PD-L1 expression leads to immune evasion. This hypothesis is supported by separate studies demonstrating that PD-L1 expressed by tumor cells enhances apoptosis of activated tumor-specific T cells in vitro and that the expression of PD-L1 protects tumor cells from the induction of apoptosis by effector T cells.[35] In NSCLC, blocking PD-L1 allows for the increase of tumor-infiltrating CD8+ T cells and an increased production of IFN-γ but no difference noted in peripheral blood CD8+ T cells when subjects with NSCLC were compared with healthy controls.[36] These high levels of PD-L1 protein expression in NSCLC have also been significantly associated with poor prognosis and the presence of tumor infiltration by immature dendritic cells.[26]

Intriguingly, preliminary data indicate that PD-L1 protein expression in tumors may correlate with nivolumab clinical activity. Archival tumor specimens from a limited subset (N = 30) of subjects in MDX1106-03 were assessed for tumor PD-L1 protein expression measured by immunohistochemistry (IHC). In this subset, 100% of subjects whose tumors lacked detectable expression of PD-L1 protein (N = 13) did not have evidence of clinical benefit (response, stable disease, or mixed response) to nivolumab, whereas subjects whose tumors were deemed PD-L1-positive (based on PD-L1 protein expression on a pre-defined threshold of tumor cells) were more likely to demonstrate clinical benefit. Despite the limited number of subjects evaluated in this initial study, our findings indicate that tumor PD-L1 protein expression status may have a profound impact on the likelihood of a patient to respond to nivolumab therapy. Because clinical benefit appeared to correlate with PD-L1 status measured in baseline, pre-treatment specimens, these data also suggest that PD-L1 expression could serve as a predictive biomarker for patient selection. As such, analysis of a larger number of samples is warranted, and evaluation of additional patients (and their tumors) enrolled in the MDX1106-03 study is ongoing.

In this trial, baseline tumor tissue will be collected for biomarker analyses. [redacted]

1.1.7 Rationale for Shortened Infusion Time

The risk/benefit profile for nivolumab has primarily been investigated using a 60 minute infusion. Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times will diminish some of this

burden. Amendment 04 will assess the risk/benefit of a shorter infusion time of 30 minutes duration for nivolumab in lung cancer patients.

Previous clinical studies of nivolumab monotherapy have used 60 minute infusion duration for nivolumab. Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In CA209010, (Phase 2, randomized, double blind, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at10 mg/kg). All the events were grade 1-2 and were manageable. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies, and all have been managed by following the safety algorithms (See Appendix 2 for Management Algorithms). 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 with the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

1.2 Research Hypothesis

High-grade (CTCAE v4.0 Grade 3-5) treatment-related select adverse events occur with a low frequency in subjects with advanced or metastatic NSCLC treated with nivolumab monotherapy.

1.3 Objectives(s)

1.3.1 Primary Objectives

To estimate the incidence of high grade (CTCAE v4.0 Grade 3-4 and Grade 5) treatment-related select adverse events in subjects with advanced or metastatic NSCLC who have progressed during or after at least one prior systemic therapy and are treated with nivolumab monotherapy.

1.3.2 Secondary Objectives

To estimate the incidence and characterize the outcome of all high grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events in subjects with advanced or metastatic NSCLC who have progressed during or after at least one prior systemic therapy and are treated with nivolumab monotherapy.

1.3.3 Exploratory Objective(s):

- To assess safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities in all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and in Cohorts A and B
- To estimate efficacy of nivolumab by measuring overall survival (OS), progression-free survival (PFS), objective response rate (ORR) based on investigator assessment, and duration of response (DOR) in all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and in Cohorts A and B (OS, PFS and DOR only)
- To explore the evolution of Patient Reported Outcomes (PRO) using the Lung Cancer Symptoms Scale (LCSS) and EQ-5D instruments in all treated subjects, by subject subgroups, and in Cohorts A and B

- To estimate the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks as measured by LCSS
- [redacted]
- [redacted]
- [redacted]

1.4 Product Development Background

Nivolumab is in clinical development for the treatment of subjects with NSCLC, renal cell carcinoma (RCC) and melanoma. The registrational development path in NSCLC is in previously treated subjects with squamous (SQ) or non-squamous (NSQ) tumor histology.

1.4.1 Mechanism of Action of Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death.

Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[37,38,39] Support for the role of immunosurveillance in NSCLC is suggested in retrospective analyses demonstrating a correlation between tumor infiltrating lymphocytes in surgically resected specimens and recurrence free survival.[40,41,42] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[43] Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA29. PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon -γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes [40]. These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ~1 nM). Nivolumab binds specifically to

PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV-re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[9]

1.4.2 Non-small Cell Lung Cancer (NSCLC) - Background and Treatments

Lung cancer is the leading cause of cancer-related deaths globally. An estimated 221,130 new cases of lung cancer will be diagnosed in 2011.[44] The majority of subjects (approximately 78%) are diagnosed with advanced or metastatic disease. Progression after first-line therapy occurred in nearly all of these subjects and the 5 year survival rate is only 3.6% in the refractory setting.[44]

There is a particular unmet need among patients who have squamous cell NSCLC (representing up to 25% of all NSCLC) as there are few treatment options after first-line therapy (ie, pemetrexed is not a treatment option.[2,45] In addition, there are targeted therapeutics that are restricted to the non-squamous population due to adverse events (ie, bevacizumab was associated with fatal hemorrhages in squamous cell subjects).[46] According to NCCN guidelines, the use of single agent chemotherapy is standard-of-care for patients with recurrent and metastatic NSCLC after failure of platinum-based therapy.[44] Historical median PFS rates in second-line NSCLC are approximately 2.6 - 3.2 months, and median OS rates approximately 6.7 to 8.3 months (longer in the recent ZODIAC trial, 10+ months).[30,31,45,47,48] Current therapy in second-line includes docetaxel, erlotinib and pemetrexed (only in non-squamous histologies).[30,31,45] No agent has shown superiority in OS when compared to docetaxel. Different docetaxel schedules (other than the standard q3 weeks), chemotherapy doublets using docetaxel, and other comparative agents have not shown improvement over docetaxel in this line of therapy.[49,50,51,52,53]

1.4.3 Nivolumab Clinical Results

Two studies contributed to most of the monotherapy clinical experience with nivolumab in subjects with malignancies. CA209001 was a Phase 1 single-dose dose escalation study in subjects (N = 39) with previously treated advanced or metastatic cancer. Subjects received a single dose of nivolumab at 0.3, 1, 3, or 10mg/kg with an option for retreatment at 3 months. MDX1106-03 is an ongoing Phase 1 open-label, multiple dose escalation study in subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC (squamous and non-squamous), colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 18 March 2013 data cut-off date, 129 subjects with NSCLC were treated. Most active doses, as measured by ORR, were 3 and 10 mg/kg. An ORR of 19% to 26% was reported with a 24-week progression free survival rate (PFSR) of 25% to 45%. Only a single response (1/33) was reported at 1 mg/kg. Durable responses were observed in both

squamous and non-squamous subtypes. ORR at 3 mg/kg and 10 mg/kg in squamous was 22% and 24%, and in nonsquamous was 26% and 19%, respectively.[9]

1.4.3.1 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in MDX1106-03. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from approximately 350 subjects from CA209001, CA209002, and MDX1106-03.

Single dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose- proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the Investigator Brochure.[9]

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from CA209001, CA209002 and MDX1106-03. Clearance (CL) of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

1.4.3.2 Safety Summary

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 1500 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs which may be numerically greater in subjects with NSCLC. In some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level.[9]

In MDX1106-03, at the data cut-off date of 18 March 2013, a total of 306 subjects were treated and 303 (99.0%) subjects have 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 frequently reported treatment-related high grade AE was fatigue (6.5%). The 10 mg/kg cohort

had numerically greater frequency of high-grade select AEs (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy).

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the IB.[9]

1.4.3.3 Anti-Tumor Activity Summary

Efficacy data from MDX1106-03 updated on 18-Mar-2013 are presented in the Investigators' Brochure.[9] All subjects initiated study treatment at least 14 months before analysis. Clinical antitumor activity was observed in heavily pretreated melanoma, RCC, and NSCLC subjects at all nivolumab doses tested. NSCLC subjects (n=129) were treated at doses of 1, 3, and 10 mg/kg. Antitumor activity was mainly observed in the 3 and 10 mg/kg dose groups, and exposure-response appeared to be relatively flat at doses ≥ 3 mg/kg. At the 3 and 10 mg/kg dose levels, the RECIST-defined objective response rates for NSCLC subjects were 24% and 20%, respectively, with no notable differences between squamous and non-squamous histologies. Among responders with NSCLC, the median duration of response was 74 weeks (range 6+ to 134 weeks). PFS rates at 24 weeks (PFSR-24) ranged from 25% to 45% at the 3 and 10 mg/kg dose levels. These preliminary data suggest that nivolumab induces substantial durable disease control in heavily pretreated subjects with NSCLC.

Nivolumab monotherapy at 3 mg/kg every 2 weeks is also being evaluated in one of several cohorts of chemotherapy-naive patients with advanced NSCLC in study CA209012. After at least 2 months of follow-up, preliminary results (data base lock 15-Apr-2013) from this cohort (n=20), including 9 squamous subjects and 11 non-squamous subjects, show an ORR of 30% (22% in squamous; 36% in non-squamous).[9]

These response rates in patients with heavily pretreated NSCLC in MDX1106-03 and in chemotherapy-naive NSCLC patients from the CA209012 study are comparable to the response rate with platinum-doublet chemotherapy. The duration of responses in the MDX1106-03 study compares favorably to chemotherapy and suggests that continued study of nivolumab in NSCLC subjects is warrented.[9]

1.5 Overall Risk/Benefit Assessment

Subjects with advanced or metastatic NSCLC who progress with first-line therapy represent a great unmet need. The clinical activity of nivolumab observed to date in NSCLC suggests the potential for improved clinical outcomes as monotherapy. Nivolumab) also has the potential for clinically relevant adverse events including liver toxicities, thyroiditis, pneumonitis, and diarrhea. However, the activity and manageable AEs profile observed with nivolumab supports a larger safety study in Stage III/IV NSCLC patient population that has progressed during or after receiving at least one prior systemic regimen.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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 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 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

In this safety study of nivolumab monotherapy, subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Eligible subjects will be treated with nivolumab administered intravenously over 30 minutes at 3 mg/kg every two weeks. Each

14 day dosing period will constitute a cycle. After 1 year (52 weeks) of treatment all subjects who are still on treatment will be randomized (1:1) to one of the two cohorts, Cohort A or Cohort B.

- Cohort A: Subjects randomized to Cohort A will continue to receive treatment until disease progression, unacceptable toxicity, or withdrawal of informed consent.
- Cohort B: Subjects randomized to Cohort B will discontinue treatment at 1 year (52 weeks). After randomization, subjects will remain on the study and will follow all study assessments [redacted]. Upon progression, subjects can receive retreatment. [redacted]
  Subjects who are retreated can continue to receive study drug until further progression, unacceptable toxicity, or withdrawal of informed consent.

Study treatment can continue beyond initial investigator assessed progression, as specified in criteria presented in Section 4.3.4 Treatment Beyond Disease Progression. The study will close after the last enrolled subject completes 5 year follow up.

The study will enroll subjects into 4 subgroups as detailed in Table 3.1-1.

Enrollment will open first to subgroup 1 only. A decision to open enrollment for each of the other subgroups 2-4 will be dependent upon the sponsor review of data from the ongoing Phase 2 and 3 studies for each patient population. The decision will take into account the overall risk/benefit profile for each patient population and the determination will be made whether or not to collect additional safety and efficacy data to supplement that already collected.

At the time of Protocol Amendment 01 (June 2014), all subgroups were opened.

Protocol Amendment 03 (November 2014) allowed for continued enrollment beyond 780 subjects in two of the study subgroups. However, as of Protocol Amendment 04 (December 2014), enrollment under Amendment 03 will stop, but enrollment will continue until 500 additional subjects are treated. Enrollment will continue until a total of 1280 subjects are treated.

[redacted]

Under Protocol Amendment 04, all subjects will receive nivolumab by IV infusion administered over 30 minutes, including new and existing subjects enrolled in the study, including subjects enrolled under Amendment 02.

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

Figure 3.1-1: Study Design Schematic

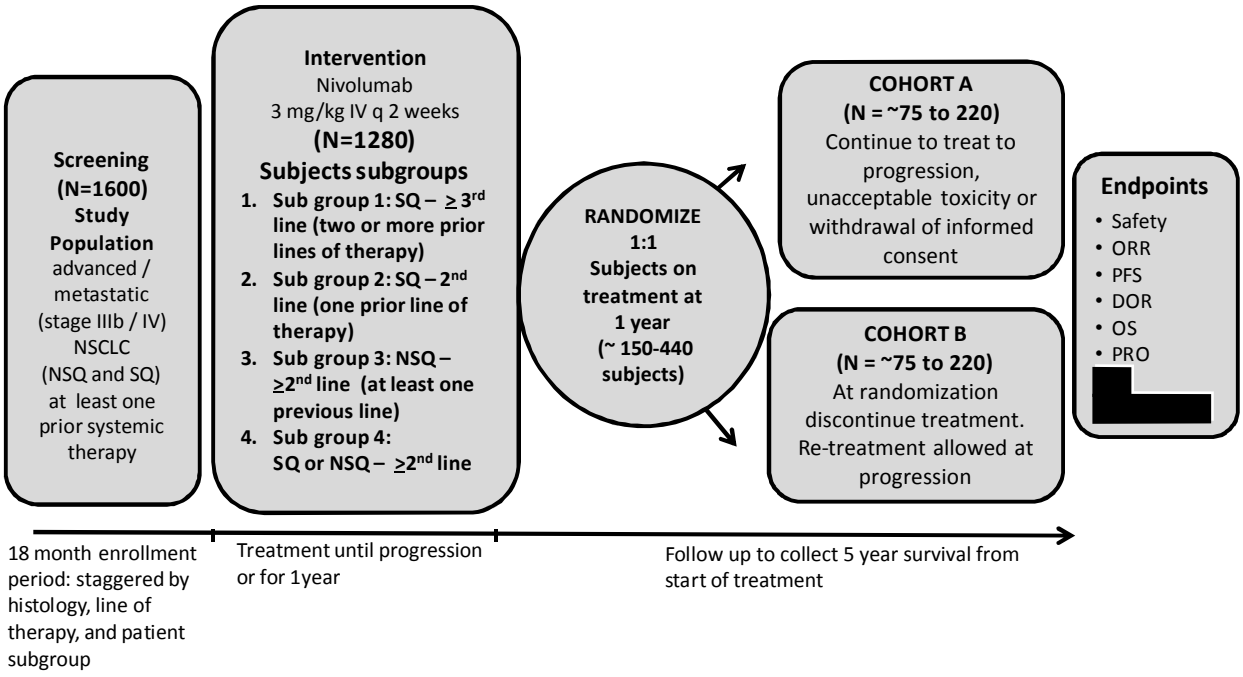


Table 3.1-1: Staggered Enrollment by Patient Subgroup

Histology (Subgroup Number)[a]	Disease Criteria	Staggered Enrollment[b,d]
Squamous (Subgroup 1)[c]	• **Failed two or more prior therapies** • PS 0-1 • Subjects with treated CNS metastases requiring no corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) are allowed	Opens at study start
Squamous (Subgroup 2)	• **Failed only one prior therapy** • PS 0-1 • Subjects with treated CNS metastases requiring no corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) are allowed	Yes
Nonsquamous (Subgroup 3)	• **Failed at least 1 prior therapy** • PS 0-1 • Subjects with treated CNS metastases requiring no corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) are allowed	Yes
Squamous[c] and nonsquamous (Subgroup 4)	• **Failed at least 1 prior therapy** • PS 2 • Subjects with treated CNS metastases requiring no corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) are allowed	Yes

[a] Subgroup number does not necessarily reflect the order in which the subgroups will be allowed to enroll.

[b] Staggered enrollment of subgroups will depend upon the sponsor review of data from the ongoing studies for each patient population. The decision will take into account the overall risk/benefit profile for each patient population and the determination for additional data to further assess the risk/benefit profile.

[c] Per Amendment 03 (November 2014), enrollment continued for subjects with squamous histology with at least 2 line of prior therapy subjects have been enrolled. Enrollment under Amendment 03 will stop when Amendment 04 starts. [redacted]

[d] Per Protocol Amendment 04 (December 2014), an additional 500 subjects will be treated in the study. The enrollment of subjects in all subgroups will continue until a total of 1280 subjects are treated on study.

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 study drug, except for Cohort B subjects who did not progress during the 5 year follow-up (4 years from randomization). 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 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) Subjects with histologically- or cytologically-documented NSCLC (SQ or NSQ) who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiotherapy for locally advanced disease).

b) Subjects must have experienced disease progression or recurrence during or after at least one systemic therapy for advanced or metastatic disease.

i) Each subsequent line of therapy must be preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.

ii) Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.

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

iv) Subjects with recurrent disease > 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, are eligible.

v) Subjects with non-squamous histology must be tested for EGFR mutations (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution) and ALK rearrangement if tests have not been previously performed.

- EGFR testing is not required if ALK or KRAS test is positive.
- ALK testing is not required if EGFR or KRAS test is positive.

Subjects who are positive on sensitizing EGFR mutations (exon 19 deletion, exon 21 mutation (L858R)) or ALK rearrangement testing, are eligible to enroll after progression from first line tyrosine kinase inhibitor (TKI) regimen.

Subjects who are positive on nonsensitizing EGFR mutation are eligible to enroll after one line of systemic therapy, which can be either TKI or chemotherapy.

Subjects are eligible if genetic test results are indeterminate or if no tumor tissue is available or accessible for testing as long as they have received one prior systemic chemotherapy.

vi) Experimental therapies when given as separate regimen are considered as separate line of therapy.

c) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 28 days of first dose of study drug) or clinically apparent disease that the investigator can follow for response per RECIST 1.1.

d) Eastern Cooperative Oncology Arm (ECOG) performance status (PS)

i) PS 0 to 1

ii) PS 2 Subgroup 4 (Table 3.1-1) only)

e) All baseline laboratory requirements will be assessed and should be obtained within 14 days (unless otherwise specified in Table 5.1-1) of first dose of study drug. Screening laboratory values must meet the following criteria

i) WBCs > 2000/µL

ii) Neutrophils > 1500/µL

iii) Platelets > 100 x 10^3/µL

iv) Hemoglobin > 9.0 g/dL

v) Serum creatinine of < 1.5 X ULN (upper limit of normal) or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)

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

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

vi) AST < 3X ULN

vii) ALT < 3X ULN

viii) Total bilirubin < 1.5X ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

f) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to starting study treatment

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

3. Age and Reproductive Status

a) Men and women, ages ≥ 18 years, inclusive

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 months post-treatment completion. The methods of contraception are outlined in Appendix 03.

e) Men who are sexually active must adhere to the contraception requirements for male subjects for the duration of treatment with nivolumab plus 7 months post-treatment completion per Appendix 03. Female partners, who are WOCBP, of male subjects who are sexually active, must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 7 months post-treatment completion. The methods of contraception are outlined in Appendix 03.

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.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

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

b) Subjects with carcinomatous meningitis.

2. Medical History and Concurrent Diseases

a) Subjects with a history of interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Subjects with COPD whose disease is controlled at study entry are allowed.

b) Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

d) Subjects who participated in either arm of the following clinical trials CA209-017, CA209-057, CA209-026, and CA184-104 or received prior treatment with anti-PD-1 or anti-PDL1 experimental agents.

e) Subjects with a history of screen failure to any PD1 or PDL1 antibody clinical trial due to PDL1 status.

f) Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy are ongoing and required during the study period with the exception of anti-estrogen/androgen therapy or bisphosphonates. Subjects with other active malignancy requiring concurrent intervention are excluded.

g) All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

h) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

3. Physical and Laboratory Test Findings

a) Any positive test for Hepatitis B virus or Hepatitis C virus indicating acute or chronic infection.

b) Known history of testing positive for Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).

4. Allergies and Adverse Drug Reaction

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

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

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6. Prohibited Treatments and/or Restricted Therapies

a) Ongoing or planned administration of anti-cancer therapies other than those specified in this study

b) Use of corticosteroids or other immunosuppressive medications as per Section 3.4.1

c) An exclusion criterion has been deleted. The numbering of subsequent criteria is maintained.

d) Treatment with any investigational agent within 14 days of first administration of study treatment

7. Other Exclusion Criteria

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

b) Prisoners or subjects who are involuntarily incarcerated

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

Eligibility criteria for 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, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women 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 judgment 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 (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care.

Prior radiotherapy must have been completed at least 2 weeks prior to starting study treatment per inclusion criteria 2g. See Section 3.4.3 for guidance on concomitant palliative radiotherapy.

3.4.2 Other Restrictions and Precautions

Subjects with active, known or suspected autoimmune disease are excluded. 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.

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

3.4.3 Permitted Therapy

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

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy.

The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving nivolumab. If palliative radiotherapy is required, then nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab. Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects receiving limited field palliative radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional nivolumab to subjects who received limited field palliative radiation should follow guidelines specified in Section 4.3.4, Treatment beyond Disease Progression.

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- After randomization in Cohort B, until disease progression when subjects are eligible for retreatment
- Other protocol specific reasons for discontinuation as specified in Section 4.3.5.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. Subjects in Cohort B continue with the on-study visit schedule (Table 5.1-2) until disease progression following retreatment or upon a decision to not receive retreatment, unacceptable toxicity, or withdrawal of informed consent. 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 treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow up

Subjects who discontinue study treatment will continue to be followed. The subjects will be followed up for select AEs beyond 100 days from the last dose of study therapy, for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.

One of the exploratory end points is overall survival and every attempt will be made to obtain survival status every 3 months until death, lost to follow-up, or withdrawal of study consent.

3.6.1 Withdrawal of Consent

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

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten BMS-936558 (nivolumab), 10 mL vials will be packaged within a carton (see Table 4.1-1), and are not subject or treatment arm specific. Vial assignments by subject will be made through the IVRS (interactive voice response system) to track usage and resupply.

As described in Section 3.1, nivolumab will be dosed intravenously at 3 mg/kg every two weeks. After 1 year (52 weeks) of treatment the subjects who are still on the study and benefiting from the therapy will be randomized (1:1) via IVRS to one of the two cohorts, Cohort A or Cohort B.

Subjects randomized to Cohort A will be treated until disease progression, unacceptable toxicity, or withdrawal of informed consent. Subjects randomized to Cohort B will discontinue treatment at 1 year (52 weeks). Subjects in Cohort B will remain on the study and will follow all study assessments [redacted]. At progression, subjects in Cohort B may receive retreatment [redacted]. Subjects who are retreated can continue until progression, unacceptable toxicity, or withdrawal of informed consent. Study treatment can continue beyond initial investigator assessed progression, as specified in criteria presented in Section 4.3.4 Treatment Beyond Disease Progression.

Table 4.1-1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 to 8° C. Protect from light, shaking, and freezing.

NOTE: Medications used to treat BMS-936558 (nivolumab)-related infusion reactions are (eg, diphenhydramine, acetaminophen/paracetamol, corticosteroids) considered NIMPs (noninvestigational products) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert. For further details related to these medications and BMS-936558 (nivolumab)-related infusion reactions, please see section 4.3.6.

4.1.1 Investigational Product

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

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

In this protocol, investigational product(s) is/are: BMS-936558 (nivolumab) Solution for Injection

4.1.2 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 medications used to treat BMS-936558 (nivolumab) related infusion reactions (see Section 4.3.6).

4.1.3 Handling 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. BMS-936558 (nivolumab) vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

Recommended safety measures for preparation and handling of BMS-936558 (nivolumab) include laboratory coats and gloves.

After BMS-936558 (nivolumab) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current BMS-936558 (nivolumab) Investigator Brochure.[9]

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936558 (nivolumab) and polyolefin bags have been observed.

BMS-936558 (nivolumab) was administered as a 60 minute IV infusion. As of Protocol Amendment 04, a 30 minute infusion will be used for all subjects; Subjects enrolled before Protocol Amendment 04 will be switched to the 30 minutes infusion. A volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses will be used. Nivolumab is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) will be found in the current Investigator brochure for BMS-936558 (nivolumab).[9]

4.2 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Also, the IVRS will be used to manage staggered enrollment of subject subgroups, and to randomize subjects at 1 year (52 weeks, ± 2 weeks) as well as to track the randomized subjects from subgroups to cohorts. Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

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

- Date of informed consent
- Date of birth
- Gender at birth
- Diagnosis (ie, SQ or NSQ NSCLC)
- Number of lines of therapy with confirmed progression
- PS

The subjects who complete 1 year (52 weeks) of study treatment and are still benefiting from the nivolumab treatment will be randomized (1:1) via IVRS to one of the two cohorts, Cohort A or Cohort B.

4.3 Selection and Timing of Dose for Each Subject

Subjects will receive treatment with nivolumab as a 30 minute IV infusion, on Day 1 of a treatment cycle every 2 weeks. Dosing calculations should be based on the body weight assessed as per Table 5.1-2. The dose should remain the same if the subject's weight is within 10% of the baseline weight. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first

cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.6.

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

Early recognition and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure:

- Suspected Pulmonary Toxicity
- Diarrhea and Colitis
- Suspected Hepatotoxicity (including asymptomatic liver function tests [LFT] elevations)
- Suspected Endocrinopathy
- Nephrotoxicity

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event, consider recommendations provided in Sections 4.3.1 to Section 4.3.3.

4.3.1 Dose Delay Criteria

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

4.3.1.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

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

4.3.2 Dose Reductions

There will be no dose modifications of nivolumab.

4.3.3 Criteria to Resume Treatment with Nivolumab

- Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions: Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- 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 should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.
- Subjects in Cohort B will also be allowed to resume treatment upon progression

Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.3.4 Treatment Beyond Disease Progression

As described in Section 1.4.3.3, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects treated with nivolumab will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease (PD) as long as the following criteria are met:

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

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

A radiographic assessment/ scan should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

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

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. Treatment should be discontinued permanently upon documentation of further disease progression

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

Subjects with global deterioration of health status who require discontinuation of treatment without objective evidence of disease progression at the time of treatment discontinuation should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie radiographic confirmation) even after discontinuation of treatment.

4.3.5 Treatment Discontinuation Criteria

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

- Nivolumab treatment should be permanently discontinued for the following:
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥3 drug-related AST, ALT or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants

continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events:
  - Grade 4 neutropenia ≤ 7 days does not require discontinuation
  - Grade 4 lymphopenia or leukopenia does not require discontinuation
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation
  - Isolated Grade 4 amylase or lipase abnormalities those are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor Medical Monitor designee should be consulted for Grade 4 amylase or lipase abnormalities.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Medical Monitor designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Sponsor Medical Monitor designee. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Medical Monitor designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

4.3.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 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 BMS 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 BMS 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.

4.6.2 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 BMS 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 (CA209153)

Procedure	Screening Visit (28 days prior to dosing unless otherwise specified)	Notes
Eligibility Assessments		
Informed Consent	X	
IVRS	X	An IVRS will be used to assign subject numbers, staggered enrollment of subject subgroups, and randomization at 1 year (52 weeks, ± 2 weeks)
Inclusion/Exclusion Criteria	X	
Medical History	X	Medical history will include smoking history. In addition, mutational status of EGFR, ALK, ROS, MET, KRAS and BRAF should be collected, if available. If mutational status is not available in the medical history of subjects with non-squamous histology, EGFR and ALK mutational status must be determined as specified in Section 3.3.1.
Safety Assessments		
Physical measurements (including performance status)	X	Includes height, weight, performance status (ECOG); baseline EKG, and a focused physical exam is to be performed at screening. C1D1 weight is to be used as baseline weight.
Vital Signs and oxygen saturation	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable). Obtain vital signs at screening visit and within 72 hours of first dose
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose, prior to study treatment initiation
Concomitant medications	X	Within 14 days of first dose
Laboratory Tests	X	Labs performed locally within 14 days prior to first dose (unless otherwise specified): CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), liver function tests (AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH). The following labs can be performed locally within 28 days prior to first dose: TSH, free T3, free T4, hepatitis B surface antigen (HBV sAg) and Hepatitis C

Table 5.1-1: Screening Procedural Outline (CA209153)

Procedure	Screening Visit (28 days prior to dosing unless otherwise specified)	Notes
		antibody (HCV Ab) or Hepatitis C RNA (HCV RNA)
Pregnancy Test	X	Within 24 hours prior to first dose for WOCBP only (serum or urine at the site).
Radiographic Tumor Assessment (Chest, Abdomen, Head)	X	Within 28 days prior to first dose. CT/MRI of brain (with contrast, unless contraindicated) required for subjects who have known history of brain metastases or if clinically indicated.. Additional sites of known or suspected disease (including pelvis) should be imaged at the screening visit.
Archived Tumor Tissue or Recent Tumor Biopsy	X	One formalin-fixed paraffin embedded tumor tissue block, or 10 minimum FFPE unstained slides are to be submitted if available. Submit a copy of the original pathology report along with the sample. Tissue samples from different biopsy procedures are to be submitted if available with each matching pathology report and biopsy date. NOTE: For subjects previously enrolled in CA 209118, tumor tissue and/or laboratory data generated from tissue collected in CA209118 is to be utilized for this study.
[redacted]		

Table 5.1-2: On-Study Procedural Outline (CA209153)

Procedure	C1D1 (Cycle 1 Day 1)	Each Cycle (Every 2 weeks) on Day 1	Every 3 Cycles (Every 6 weeks) on Day 1	Every 4 Cycles (Every 8 weeks) on Day 1	Notes
Safety Assessments					
Vital Signs and oxygen saturation[a]	X	X			Within 72 hours prior to dosing. Include temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest prior to dosing and at any time there are new or worsening respiratory symptoms. (see Section 5.3.2) Patients randomized to Cohort B will be assessed every 2 or 4 weeks for clinical assessment and physical examination per investigator decision. If nivolumab is restarted, every two week assessment schedule must be resumed.
Adverse Events Assessment	Continuously				Continuously assessed using NCI CTCAE v. 4.0.
Physical measurements and target physical exam (including Performance Status)	X	X			Includes weight, ECOG status, and targeted physical exam as clinically indicated Patients randomized to Cohort B will be assessed every 2 or 4 weeks for clinical assessment and physical examination per investigator decision. If nivolumab is restarted, every two week assessment schedule must be resumed.
Laboratory Tests[b]					Cohort B: For subjects randomized to Cohort B, lab tests will be performed every 4 weeks. If nivolumab is restarted, every two week lab assessment schedule must be resumed.

Table 5.1-2: On-Study Procedural Outline (CA209153)

Procedure	C1D1 (Cycle 1 Day 1)	Each Cycle (Every 2 weeks) on Day 1	Every 3 Cycles (Every 6 weeks) on Day 1	Every 4 Cycles (Every 8 weeks) on Day 1	Notes
Complete blood counts (CBC) (Obtain results prior to dosing on infusion days)	X	X			Screening labs performed within 14 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing. Tests include WBC count with differential, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count
Serum chemistry (Review results prior to dosing on infusion days)	X	X			Screening labs performed within 14 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing. BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, and LDH
Liver function (Review results prior to dosing on infusion days)	X	X			Screening labs performed within 14 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin
Thyroid function	X		X*		Screening labs performed within 28 days of C1D1 visit unless clinically indicated. TSH (reflex to free T3 and free T4 if abnormal result) Thyroid function test may be performed within 72 hours prior to dosing. *Cohort B: TSH/thyroid function tests can be done every 12 weeks.

Table 5.1-2: On-Study Procedural Outline (CA209153)

Procedure	C1D1 (Cycle 1 Day 1)	Each Cycle (Every 2 weeks) on Day 1	Every 3 Cycles (Every 6 weeks) on Day 1	Every 4 Cycles (Every 8 weeks) on Day 1	Notes
Pregnancy Test	X		X		Serum or urine test for WOCBP only, to be performed C1D1 and every 6 weeks, or more frequently as required by local standards. Serum or urine test may be performed within 24 hours of scheduled dose.
Review of concomitant medications	X	X			At each visit
Efficacy Assessments					
Radiographic tumor assessments				X	At Week #9 (the 9th week on study with C1D1 week counted as week #1) ± 5 days and every 8 weeks (± 5 days) thereafter up to 24 months from first dose then every 12 weeks (± 5 days) regardless of dosing schedule, until documented disease progression or discontinuation of study therapy in subjects receiving nivolumab beyond progression. Assessments should include all areas that are being monitored and new areas if clinically indicated (with contrast unless contraindicated). Follow RECIST 1.1 criteria. Subjects with a history of brain metastasis (BM) should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated. After 24 months of treatment, the frequency of surveillance brain MRI or CT scans will be every 6 months or earlier, if clinically indicated, for subjects with known brain metastases.

Table 5.1-2: On-Study Procedural Outline (CA209153)

Procedure	C1D1 (Cycle 1 Day 1)	Each Cycle (Every 2 weeks) on Day 1	Every 3 Cycles (Every 6 weeks) on Day 1	Every 4 Cycles (Every 8 weeks) on Day 1	Notes
[redacted]					
Randomization	At 1 year (52 weeks)				Subjects that are still on study and benefiting from treatment will be randomized 1:1 to Cohort A or B.

Table 5.1-2: On-Study Procedural Outline (CA209153)

Procedure	C1D1 (Cycle 1 Day 1)	Each Cycle (Every 2 weeks) on Day 1	Every 3 Cycles (Every 6 weeks) on Day 1	Every 4 Cycles (Every 8 weeks) on Day 1	Notes
Administration of nivolumab (BMS-936558) 3 mg/kg	X	X			All subjects start treatment on C1D1 and continue treatment every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of informed consent. At 1 year (52 weeks) all subjects that remain on treatment will be randomized to Arm A or Arm B. Cohort A subjects will continue treated until disease progression, unacceptable toxicity, or withdrawal of informed consent. Cohort B subjects will discontinue treatment at 1 year (52 weeks ± 2 weeks). Upon progression, subjects can be retreated until progression, unacceptable toxicity, or withdrawal of informed consent. Treatment for all subjects can continue beyond initial investigator-assessed progression as specified in Section 4.3.4. Drug administration is +/- 3 days but no less than 12 days from previous dose. Study drug infusion start and stop times will be recorded. .
LCSS and EQ-5D	X		X		Complete every 3 cycles (every 6 weeks) on Day 1 during first 1 year (52 weeks) of treatment. After randomization at one year (52weeks), every other cycle on Day 1. Complete assessments prior to any contact with study staff if possible

[a] Monitor amount of supplemental oxygen if applicable. If a subject shows changes in oxygen saturation or supplemental oxygen requirement, or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, immediately evaluate to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm provided in the Investigators' Brochure.

[b] Review serum chemistry and liver function prior to dosing. Perform CBCs prior to dosing but results need not be reviewed prior to dosing.

Table 5.1-3: Follow-up Procedural Outline (CA209153)

Procedure	Initial Follow-Up Phase (100 days from the date of last study treatment) Follow-up Visit 1 (X01) and Visit 2 (X02)	Further Follow-up Phase (beyond X02)	Notes
			• **Subjects who discontinue treatment prior to randomization and subjects in Cohort A**: Follow-up Visit 1 (X01) is to occur 30 days (± 5 days) after last dose or coinciding with the date of discontinuation (± 5 days) if date of discontinuation is greater than 35 days after last dose. • **Subjects in Cohort B**: Follow-up Visit 1 (X01 is to occur 30 days (± 5 days) after disease progression and a decision has been made to not retreat the subject or at 30 days (± 5 days) of discontinuation after retreatment • Follow up Visit 2 (X02) is to occur approximately 70 days (± 5 days) after X01
Radiographic Tumor Assessment	X	X	For subjects who discontinue study treatment for reasons other than PD, follow up scans (or MRIs when appropriate) should be performed every 8 weeks (± 5 days) up to 24 months from first dose then every 12 weeks (± 5 days) until PD, death, lost to follow-up, or withdrawal of consent; radiographic assessments should not delayed until the X01 or X02. After 24 months of treatment, the frequency of surveillance brain MRI or CT scans will be every 6 months or earlier, if clinically indicated for subjects with known brain metastases.
[redacted]			
Safety Assessments			
Vital Signs	X		
Physical measurements	X		Includes performance status (ECOG)
Adverse Events Assessment	X	X	*Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.

Table 5.1-3: Follow-up Procedural Outline (CA209153)

Procedure	Initial Follow-Up Phase (100 days from the date of last study treatment) Follow-up Visit 1 (X01) and Visit 2 (X02)	Further Follow-up Phase (beyond X02)	Notes
			• **Subjects who discontinue treatment prior to randomization and subjects in Cohort A**: Follow-up Visit 1 (X01) is to occur 30 days (± 5 days) after last dose or coinciding with the date of discontinuation (± 5 days) if date of discontinuation is greater than 35 days after last dose. • **Subjects in Cohort B**: Follow-up Visit 1 (X01 is to occur 30 days (± 5 days) after disease progression and a decision has been made to not retreat the subject or at 30 days (± 5 days) of discontinuation after retreatment • Follow up Visit 2 (X02) is to occur approximately 70 days (± 5 days) after X01
Laboratory Tests	X		CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose), liver function (AST, ALT, total bilirubin, alkaline phosphatase, LDH), thyroid function (TSH, reflex to free T3 and free T4 if abnormal result)
Review of concomitant medications	X		
Pregnancy testing	X		
EQ-5D	X	X	Beyond 100 days from the last dose of study therapy, the EQ-5D will be administered every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local IRB
Collection of Survival Information	X	X	Every 3 months until death, lost to follow-up, or withdrawal of study consent for 5 years following start of therapy. May be performed by phone contact or office visit.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood [redacted] and tissue specimens
- Site manual for operation of interactive voice response system (for study enrollment)
- Serious Adverse Event (or eSAE) case report forms
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- PRO manual

Each site will be provided with PRO questionnaires. Subjects will complete these at the time of the scheduled visits, prior to any study procedures and study drug infusion. During the survival follow-up period beyond X02, the EQ-5D PRO will be administered at a frequency of every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law. (see schedule Table 5.1-2 and Table 5.1-3 for frequency of assessments).

5.3 Safety Assessments

5.3.1 Screening Assessments

Screening assessments and procedures must be completed in accordance with Table 5.1-1.

5.3.2 On-Study Safety Assessments and Procedures

The following assessments will be monitored as specified in Table 5.1-2 starting on Cycle 1 Day 1 (C1D1) and will continue at the specified frequency until discontinuation from the study.

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing. Obtain prior to dosing and at any time a subject has any new or worsening respiratory symptoms. If a subject shows changes in oxygen saturation or supplemental oxygen requirement, or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the Investigator's Brochure and in Appendix 2 for the suspected pulmonary toxicity management algorithm.

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

[redacted]

For subjects who discontinue study treatment due to toxicity, please follow the procedures for the last scheduled visit on study treatment (prior to discontinuation of study therapy and follow-up visits) from either Table 5.1-2 or Table 5.1-3 [redacted].

5.3.3 Follow-up and Survival Procedures

Subjects will be monitored for safety according to Table 5.1-2 and Table 5.1-3.

5.3.4 Imaging Assessment for the Study

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

5.4 Efficacy Assessments

5.4.1 Screening (Baseline visit) and On-Study Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1-1 and Table 5.1-2, according to RECIST 1.1 criteria.[54] High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of start of study treatment. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in subjects with a known history of treated brain metastases. 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 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 determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated. After 24 months of treatment, the frequency of surveillance brain MRI procedures will be every 6 months or earlier, if clinically indicated for patients with brain metastases.

Radiographic tumor assessments will be conducted at Week 9 (± 5 days) and every 8 weeks (± 5 days) thereafter through 24 months of treatment, disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of study consent. After 24 months of treatment, tumor assessments will take place regularly every 12 weeks (±5 days) until the end of treatment, disease progression (or

until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of study consent. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 1 for details of RECIST 1.1).

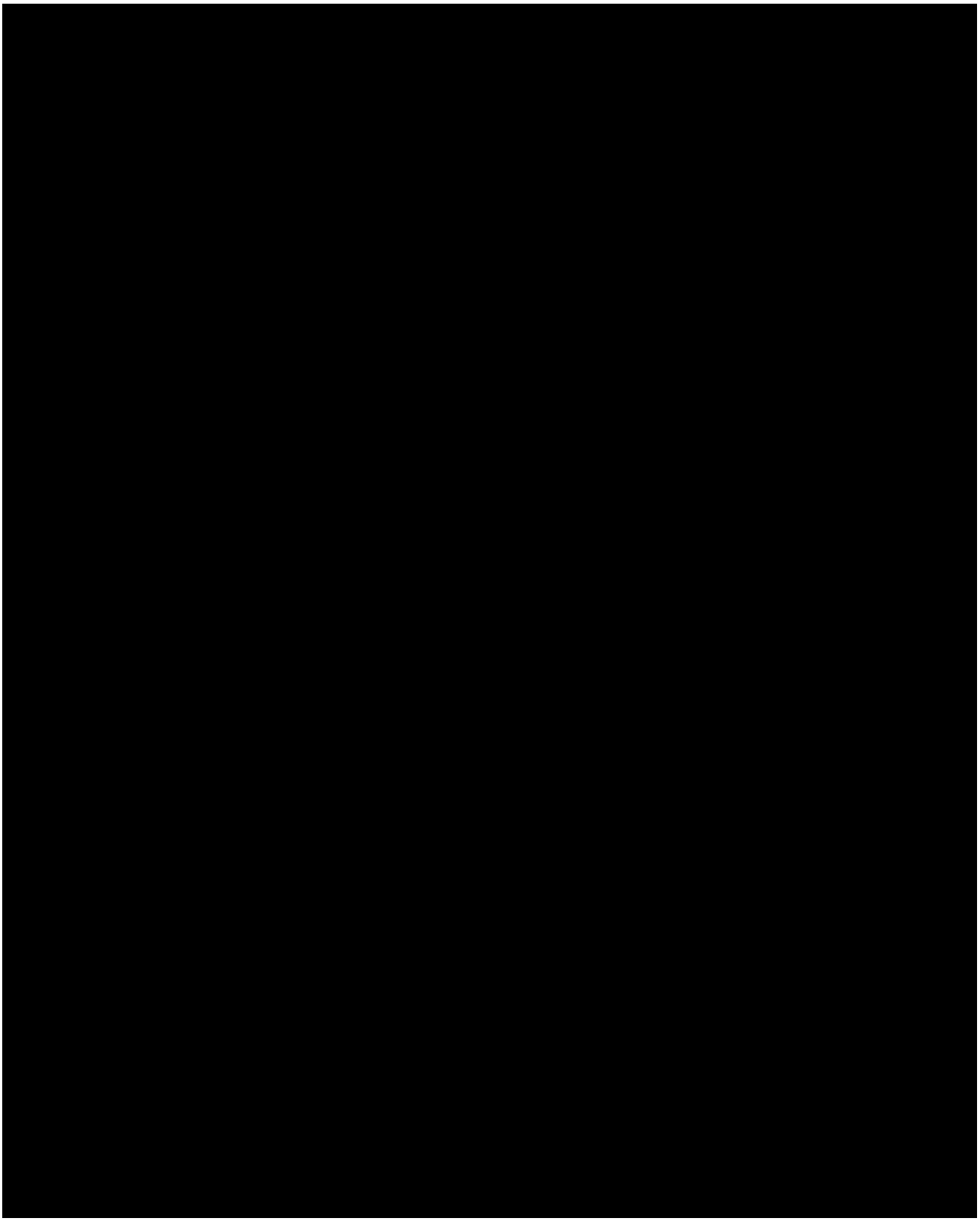
5.4.2 Follow-up and Survival Procedures

Subjects who discontinue study treatment prior to progression, and subjects being treated beyond disease progression, will be followed with radiographic tumor assessments every 8 weeks (± 5 days) until 24 months of treatment, documented or further disease progression, withdrawal of study consent, or subjects are lost to follow-up. After 24 months of treatment in these subjects, radiographic tumor assessments will be every 12 weeks (±5 days) until documented or further disease progression, withdrawal of study consent, or lost to follow-up.

Radiographic assessments should be performed according to Section 5.4.1.

Survival will be followed after progression, either by direct contact (office visits) or via telephone contact, according to Table 5.1-3 until death, withdrawal of study consent, or lost to follow-up for five years following start of therapy.

[redacted]



5.7 Outcomes Research Assessments

Patient reported outcomes (PRO) will be measured according to Table 5.1-2 and Table 5.1-3, using the following two validated subject self-reported questionnaires: Lung Cancer Symptom Scale (LCSS), and EuroQOL Group's EQ-5D.

Subjects will be asked to complete questionnaires before any clinical activities are performed during visits to the study clinics at on-study visits, and at the designated study visits in the follow-up (post-treatment) phase of the study.

Questionnaires will be provided in the subject's preferred language.

5.8 Other Assessments

Not applicable.

5.9 Results of Central Assessments

Not applicable

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (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).

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).

6.1.1 Serious Adverse Event Collection and 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).

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. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports 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).

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

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

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

6.7 Other Safety Considerations

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

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

The sponsor of this study will not utilize an independent data safety monitoring board (DSMB). BMS will assign a physician responsible for reviewing, on a systematic and continuous basis, the safety of subjects on this study. This includes a review of serious and non-serious adverse events, and all hematological and non-hematological events. In addition, BMS has a Medical Surveillance Team (MST), independent from the clinical medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk mitigation activities to ensure the safety of patients participating in BMS trials. The MST is also responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab (BMS-936558) safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

In general, for nivolumab monotherapy, the safety profile to date is similar across tumor types, while select treatment related adverse events of high grade (Grade 3-4) are rather uncommon. Their overall incidence was 6% in a previous Phase 1 trial that tested nivolumab at doses between 0.1 mg/kg to 10 mg/kg in 306 subjects with different recurrent or refractory malignancies (MDX-03). The incidence observed for similar AEs 0% in NSCLC subjects (n=129) was 0% for skin and renal AEs, and endocrinopathies; 1% gastro-intestinal, hepatic and infusion reaction AEs, and 2% for pulmonary events.[7]

In order to further characterize the frequency and outcome of such apparently infrequent safety events, the current study will treat with nivolumab approximately 780 subjects who have advanced or metastatic NSCLC and have progressed during or after at least one prior systemic regimen. This sample size will allow for estimating an incidence rate of 0.5% (n=4 subjects with events) with a 95% CI (confidence interval) of (0.14%, 1.31%), or an incidence rate of 2% (n=16 subjects with events) with a 95% CI of (1.18%, 3.31%). Furthermore, the sample size will allow for enough events such that the outcome of these rare events can be characterized.

Estimated 95% confidence intervals for various event rates for an overall population of 780 subjects, and for different size subpopulation are described in Table 8.1-1.

Table 8.1-1: Estimated Incidence Rates and 95% Confidence Intervals for the Overall Study Population and Subpopulations

Sample Size	Incidence Rate (%)	Lower 95% CI (%)	Upper 95% CI (%)
780	0.5	0.14	1.31
780	1.0	0.44	2.01
780	2.0	1.18	3.31
780	5.0	3.58	6.77
400	1.0	0.27	2.54
400	2.0	0.87	3.90
400	5.0	3.08	7.62
300	1.0	0.21	2.89
300	2.0	0.74	4.30
300	5.0	2.83	8.11
200	1.0	0.12	3.57
200	2.0	0.55	5.04
200	5.0	2.42	9.00
100	2.0	0.24	7.04
100	5.0	1.64	11.28
100	10.0	4.90	17.62

CI: confidence interval

SAS 9.2 was used to generate the 95% exact confidence intervals.

8.1.1 Sample Size at Randomization

This study also includes a randomization step reserved to subjects who received nivolumab for 1 year. In MDX1106-03, 27% of NSCLC subjects (10 of 37) were still free from disease progression at 48 weeks [95% CI of (12.7%, 41.3%)]. In the present study any subjects (all subgroups included) who are still benefiting from therapy after 1 year (estimated to be between 99 and 322 subjects) will be randomized in order to continue treatment without any change in Cohort A (until progression, toxicity or withdrawal of consent), or to discontinue treatment in Cohort B, respectively. In the latter subjects will have the option of retreatment should progression occur.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IVRS.
- All treated subjects: all subjects who received any nivolumab. This is the primary population for safety and efficacy analyses. Subpopulation analyses will be conducted by

tumor histology (SQ or NSQ), by subject subgroups (subgroup 1 to 4), and for Cohorts A and B.

- All randomized subjects: all subjects who were randomized to Cohort A or B after completing 1 year of treatment.
- All response evaluable subjects: all treated subjects who have baseline and at least one on-study evaluable tumor measurement.
- [redacted]
- [redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective of the study will be assessed by measuring the incidence for high grade (Grade 3-4 and Grade 5) treatment related select adverse events.

8.3.2 Secondary Endpoint(s)

The secondary objective of the study will be assessed by measuring the following:

- incidence for high grade (Grade 3-4 and Grade 5) select adverse events
- median time to onset, median time to resolution (Grade 3-4)
- percentage of subjects who received immune modulating medication (e.g. corticoidsteroids, infliximab, cyclophophamide, IVIG, and mycophenolate mofetil), or hormonal replacement therapy, the percentage of subjects who received ≥ 40 mg prednisone equivalents, total duration of all immune modulating medications given for the select event.

8.3.3 Exploratory Endpoint(s)

Safety and tolerability will be measured by the incidence of all adverse events, serious adverse events, deaths and laboratory abnormalities. Adverse event assessments and laboratory tests will be performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

Efficacy data will be assessed by measuring OS, DOR, ORR and PFS. These endpoints are defined as follows:

- OS is defined as the time from first dosing date 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 treatment and every 3 months via in-person or phone contact after subjects discontinue the study drug.
- DOR is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. DOR will only be evaluated in subjects with objective response of CR or PR.
- Objective response rate (ORR) is defined as the number and percentage of subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR).

Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.

- Progression-free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first. 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 first dosing date.

PRO data will be assessed by measuring change from baseline of the EQ-5D and LCSS scores at each assessment point, and disease-related symptom improvement rate at week 12 measured by LCSS.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects and all randomized subjects for Cohorts A and B.

8.4.2 Primary Analyses

The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) treatment related select adverse events will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) treatment related select adverse events will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

8.4.3 Secondary Analyses

The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) select adverse events will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) select adverse events will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

Additional descriptive statistics will include median values using the Kaplan-Meier (KM) product-limit method with 95% CI using Brookmeyer and Crowley method of time to onset and time to resolution, and will be presented for all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the

AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

Management of high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events will be characterized by measuring percentage of subjects who received immune modulating medication (or hormonal replacement therapy), percentage of subjects who received ≥ 40 mg prednisone equivalents, and total duration of all immune modulating medications given for the event, in all treated subjects who have experience high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) select adverse events, by tumor histology (SQ or NSQ), and also by subject subgroups, and all randomized subjects in Cohorts A and B.

8.4.4 Exploratory Analyses

8.4.4.1 Safety Analyses:

All safety data will be summarized and listed for all treated subjects. All on-study AEs, SAEs, treatment-related AEs, and treatment-related SAEs will be summarized using worst grade per NCI CTCAE v4.0 by system organ class and preferred term. On-study lab abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

Descriptive statistics of safety (AE and lab data) including incidence, median values using the Kaplan-Meier (KM) product-limit method with 95% CI using Brookmeyer and Crowley method of time to onset and time to resolution, and rate of discontinuation due to event occurrence will be presented for all treated subjects, by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

8.4.4.2 Efficacy Analyses

OS and PFS will be summarized by KM product-limit method for all treated subjects and all response evaluable subjects, respectively. Median values of OS and PFS, along with two-sided 95% CI using Brookmeyer and Crowley method, will be calculated. Survival rates at 6, 12, 18 and 24 months will also be estimated using KM estimates on the OS curve for all treated subjects. Associated two-sided 95% CIs will be calculated using the Greenwood formula. This analysis will be performed for all treated subjects or for all response evaluable subjects for PFS. This analysis will also be performed by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B.

The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects. This analysis will also be performed by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B.

The assessed DOR will be summarized for all response evaluable subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. In addition, the percentage of responders still in response at different time points (3, 6, 12, 18, and 24 months and at end of study) will be presented based on the DOR KM plot. This analysis will be performed for all response evaluable subjects who achieve confirmed PR or CR. This analysis will also be performed by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B.

8.4.4.3 Patient Reported Outcomes

The LCSS completion rates, defined as the proportion of questionnaires actually received out of the expected number will be calculated and summarized at each assessment point. The EQ-5D (with two essential components: the EQ-5D descriptive system and the EQ visual analogue scale - EQ VAS) will be used to assess the subject's overall health status. The baseline and change from baseline of the EQ-5D and LCSS scores at each assessment point will be summarized using descriptive statistics. The disease-related symptom improvement rate at week 12 as measured by LCSS and its corresponding 95% CI will also be calculated by Clopper-Pearson method. All summaries for LCSS and EQ-5D will be done for all treated subjects, and also by tumor histology (SQ or NSQ), by subject subgroups, and all randomized subjects for Cohorts A and B.

[redacted]

8.5 Interim Analyses

There will be no formal interim analyses.

Data cuts for publication purposes will be performed until all subjects have completed the study, which is defined as the time point when the last subject enrolled had the opportunity for five year OS follow-up.

The final analysis will be performed when all subjects have completed the study,

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

9.1.2 Monitoring

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

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

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

9.1.3 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 investigational product (those supplied by BMS) is maintained at each study site where study drugs are inventoried and dispensed. 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

The Principal Investigator will be the signatory for the clinical study report.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
HCG	Human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CI	confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form, paper or electronic
CYP	cytochrome p-450
dL	deciliter
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus

Term	Definition
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IHC	immunohistochemistry
IU	International Unit
IV	intravenous
kg	kilogram
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NSQ	Nonsquamous
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1

Term	Definition
PD-L1	Programmed death- ligand 1
PK	pharmacokinetics
PR	Partial response
PRO	Patient reported outcomes
PS	Performance status
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SQ	Squamous
T-HALF	Half life
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[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 lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

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.

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 patient, these are preferred for selection as target lesions.

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.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered 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.

1.2 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 performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT 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.

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.

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 noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

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.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

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

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

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.

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. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should not be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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 '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 (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **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 (eg, 2 mm). If the radiologist is able to provide an actual measure, 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:

i. if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

ii. 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).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have 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).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient 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 qualify for unequivocal progression status.
- When the patient 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 patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute 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 new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 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 patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

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

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

Table 1: Appendix Table 1 - Summary of the Overall Response Status Calculation [Time point response - patients with target (+/-) non-target disease]

Target lesions	Non-target lesions	New lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually 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 change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best overall response: all timepoints

Best response determination in trials where confirmation of complete or partial response IS required: 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. In this circumstance, the best overall response can be interpreted as in Appendix Table 2.

Table 2: Appendix Table 2 - Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

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

4.4 Special notes on response assessment

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

Patients with a 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 even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1 and Table 2.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

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.

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).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.
b. 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 progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009); 45:228-247.

APPENDIX 2 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

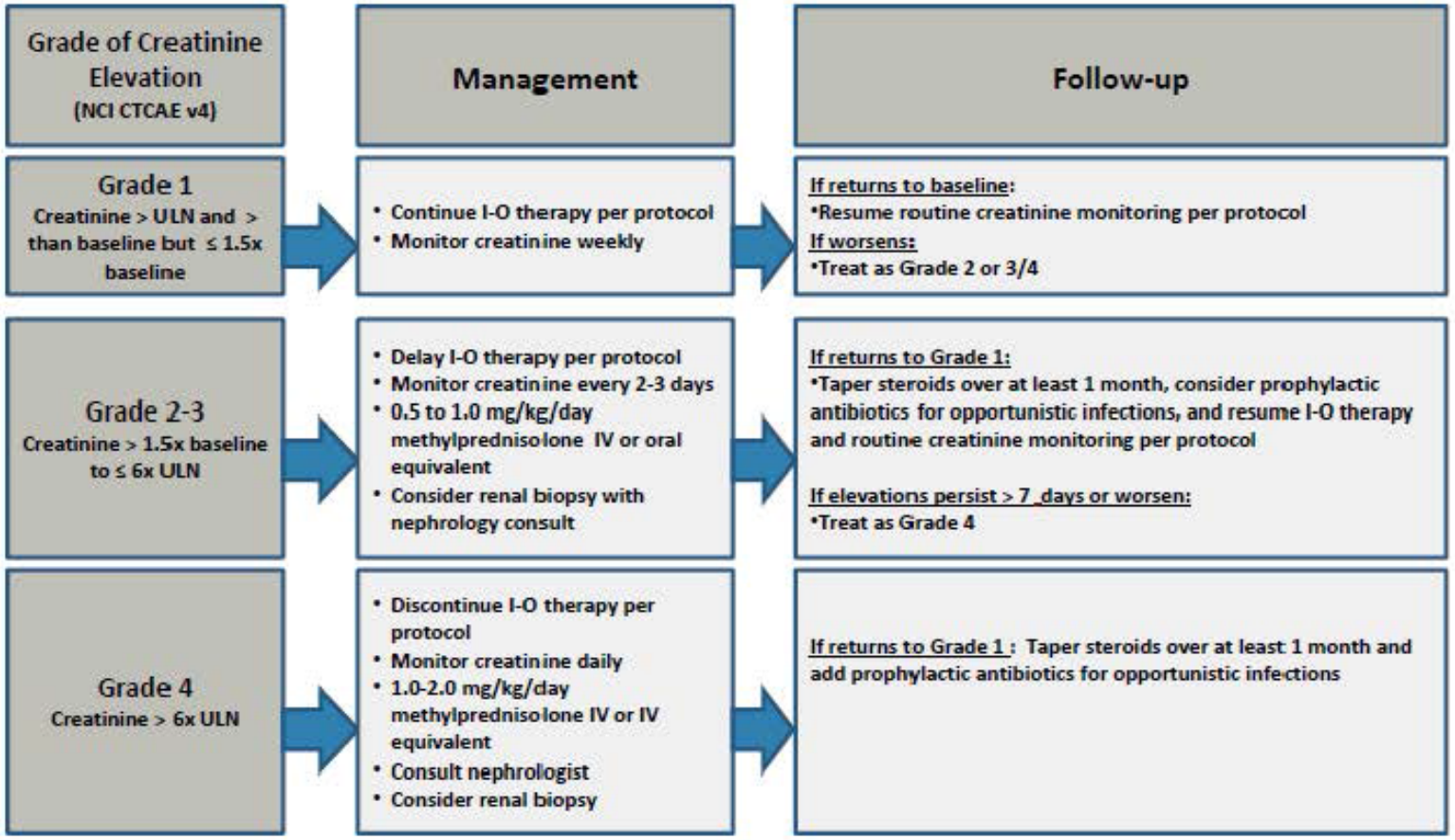
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat 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

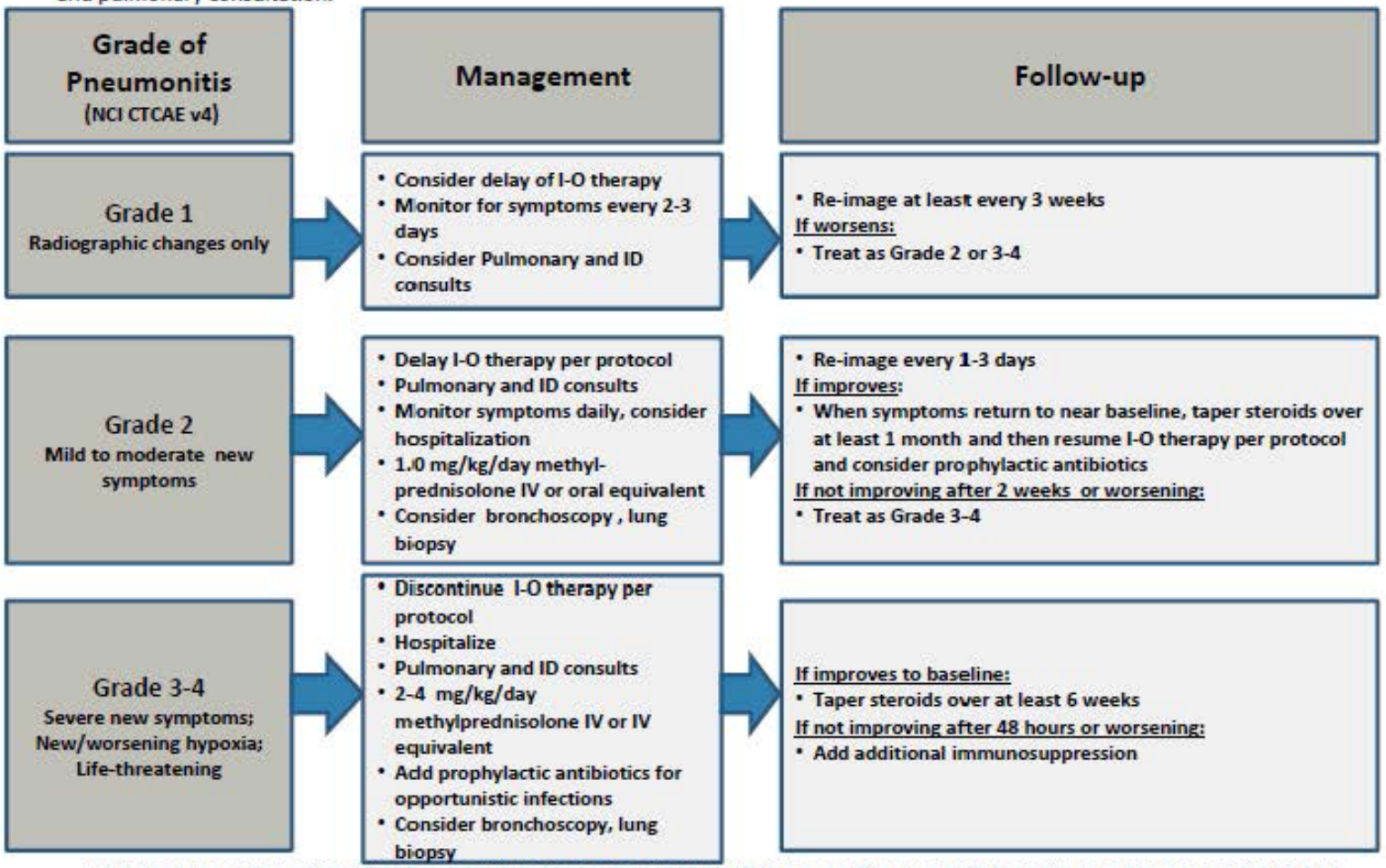


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants 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.

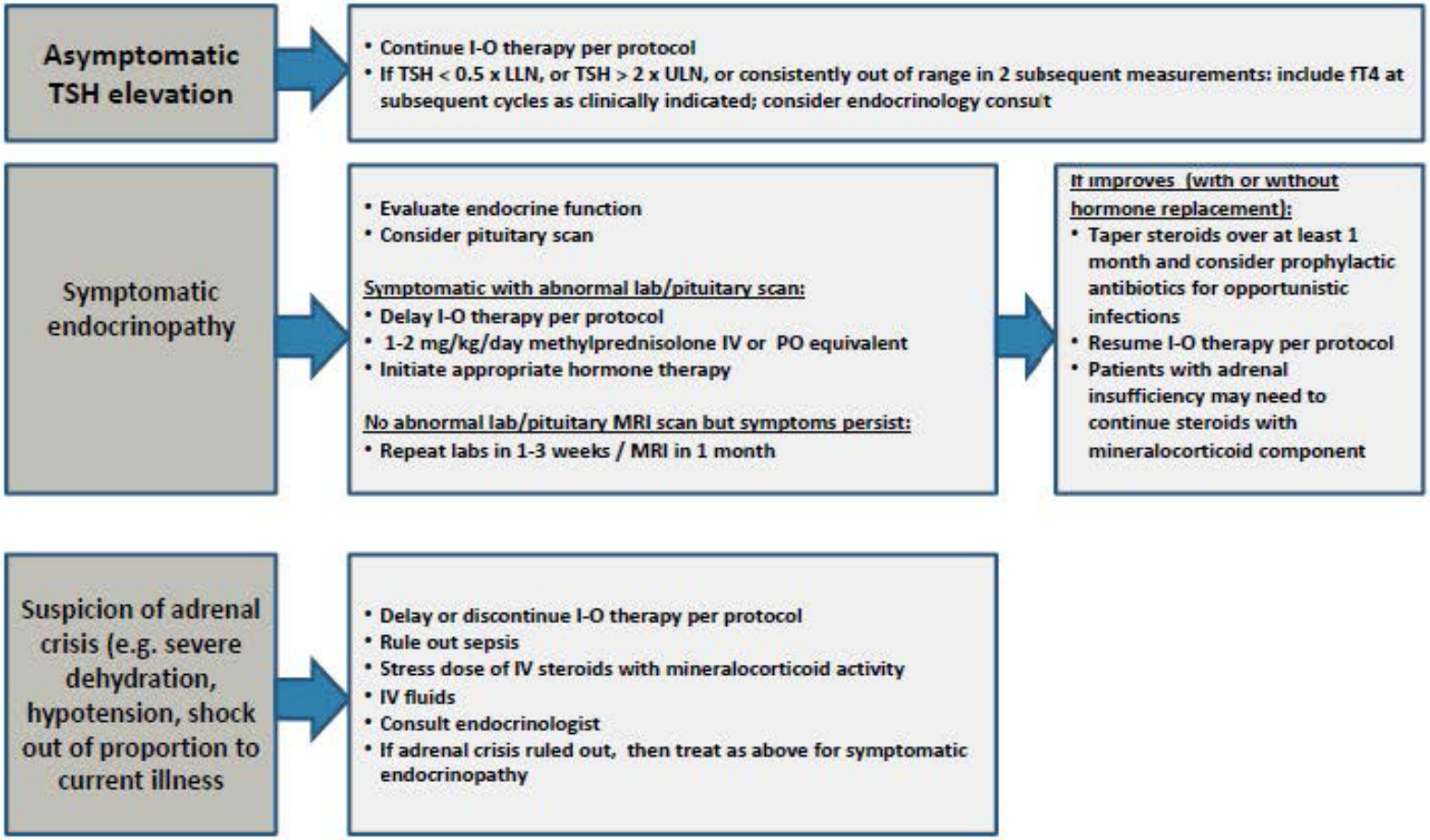
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

**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.

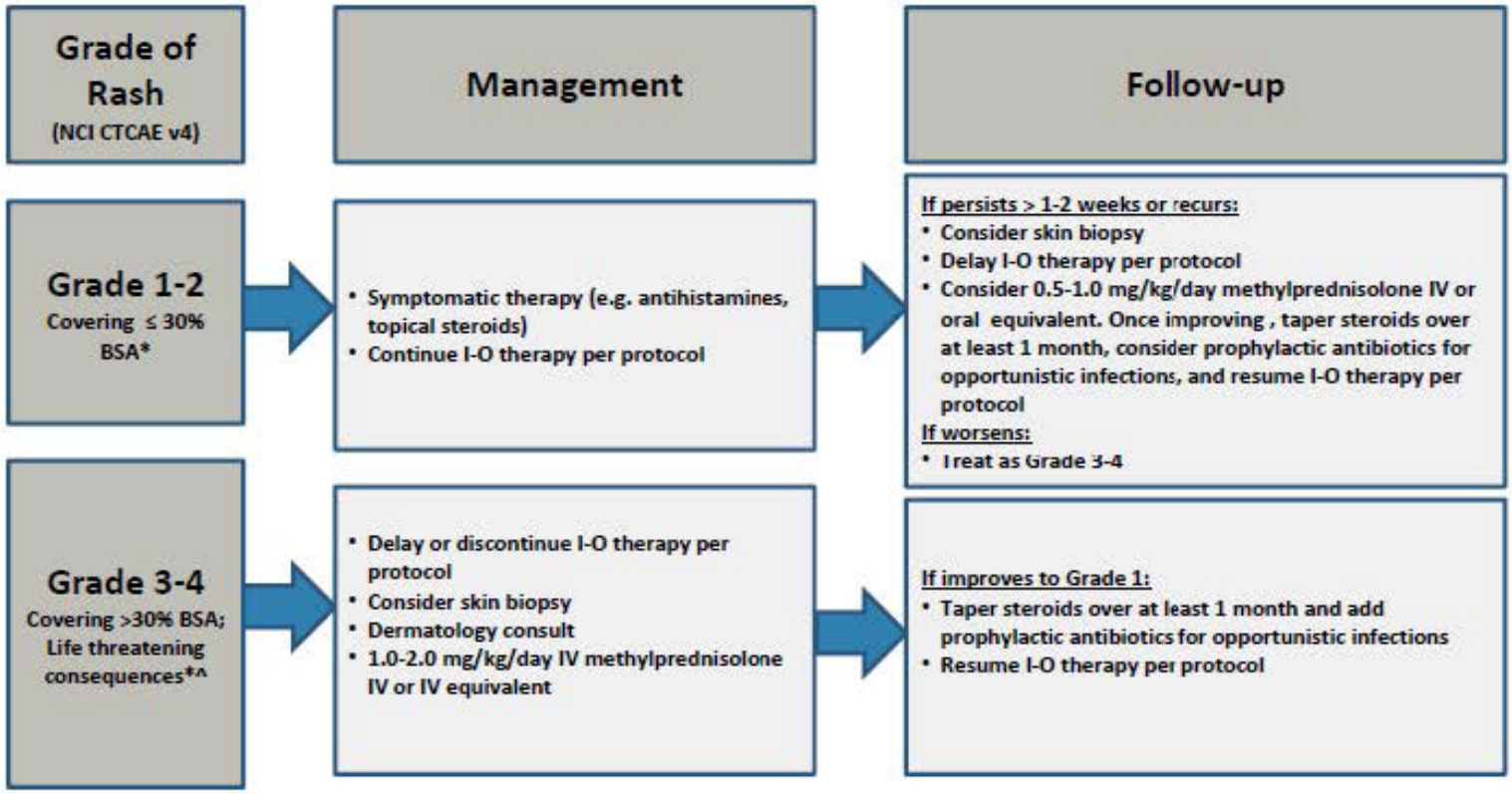


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

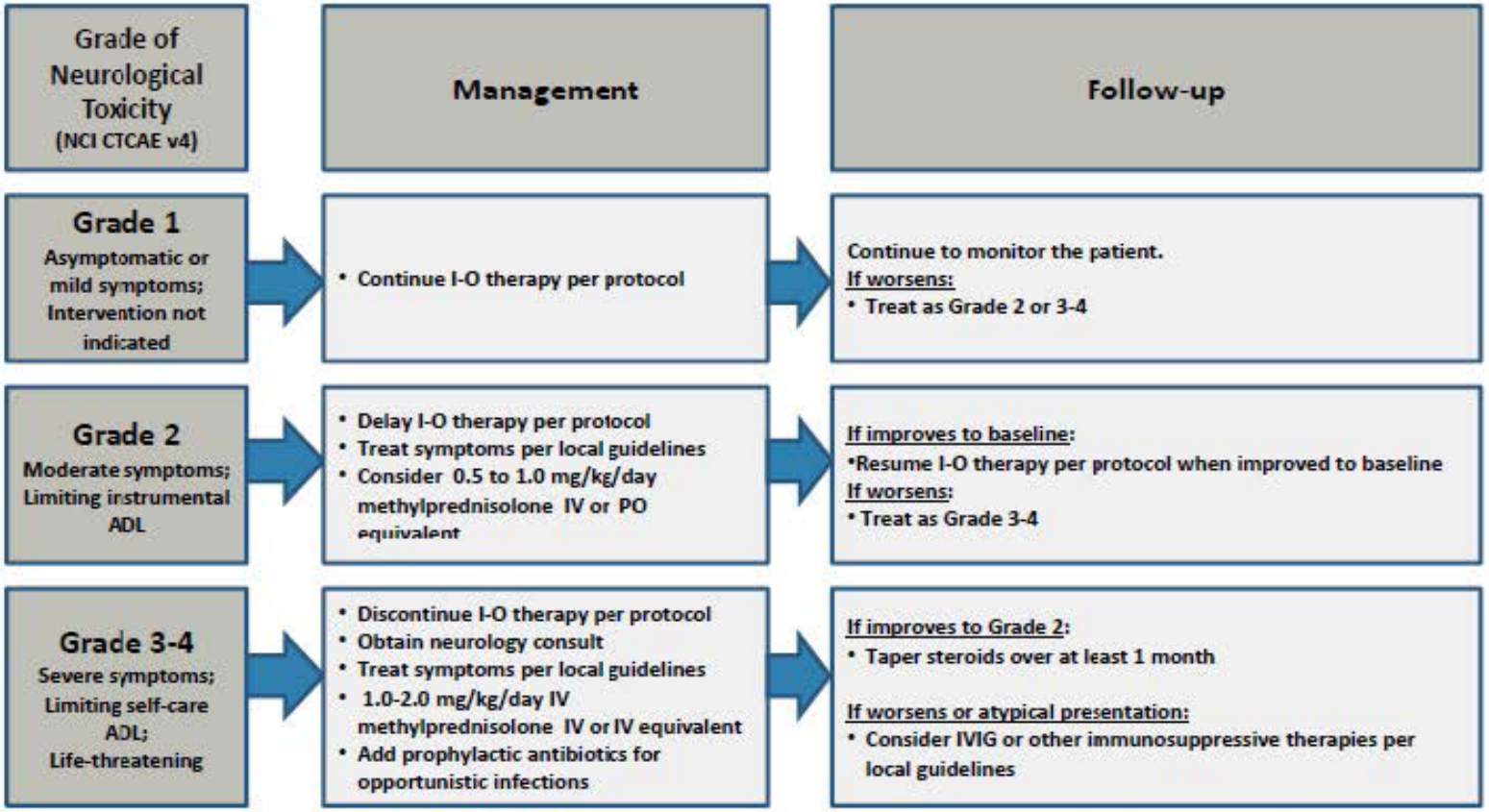


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



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 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and according to the Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.