Official Title of Study:

A Phase 1/2, Open-Label Study of Nivolumab (BMS-936558) in Chinese Subjects With Previously Treated Advanced or Recurrent Solid Tumors (CheckMate 077: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 077)

NCT Number: NCT02593786

Document Date (Date in which document was last revised): August 15, 2018

Protocol Number: CA209077
IND Number: Non-IND
EUDRACT Number N/A
Date: 04-Mar-2013
Revised Date 15-Aug-2018

CLINICAL PROTOCOL CA209077

A Phase 1/2, Open-Label Study of Nivolumab (BMS-936558) in Chinese Subjects with Previously Treated Advanced or Recurrent Solid Tumors

CheckMate 077: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 077

Revised Protocol Number: 06

Study Director/Medical Monitor

[redacted]

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

Bristol-Myers Squibb Research and Development
1717 West Nanjing Road
Shanghai 200040, P.R. China

protocol may apply to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).

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 06	15-Aug-2018	• Cohort D target population changed from nasopharyngeal carcinoma to solid tumors. • [redacted] • Updates to Management of Safety Algorithms in Appendix 1 • Sample size change in cohorts C and D from 12 subjects to "up to" 12 subjects.
Revised Protocol 05	07-Sep-2016	Incorporates Amendments 01, 02, 03, 04, & 05, Administrative Letter 01
Amendment 05	07-Sep-2016	• Incorporates updates on duration of contraception • Removal of less effective method of contraception and addition of progestogen only hormonal contraception • Updates to Adverse event management algorithm in Appendix 1 • To make any typographical edits, format updates and clarifications identified within and throughout the protocol
Revised Protocol 04	11-Apr-2016	Incorporates Amendment 01, 02, 03, & 04, Administrative Letter 01
Amendment 04	11-Apr-2016	Addition of 240 mg, 360 mg, and 480 mg flat dosing regimens in cohort expansion phase. Tumor type requirement changed to include all solid tumors at 3 mg/kg, 240 mg and 360 mg, and nasopharyngeal carcinoma at 480 mg in expansion. Infusion time changed from 60 minutes to 30 minutes in cohort expansion phase.
Administrative Letter 01	04-Dec-2015	[redacted]
Revised Protocol 03	16-Sep-2015	Incorporates Amendment 01, 02, & 03
Amendment 03	16-Sep-2015	Include tumor types in addition to non-small cell lung cancer, gastric, nasopharyngeal, esophageal cancer. Provide recent clinical/safety information following the availability of additional study results for Nivolumab. Implement the latest changes from the program protocol template as well as latest updates from the standard protocol model document.
Revised Protocol 02	01-May-2014	Incorporates Amendment 01 & 02
Amendment 02	01-May-2014	The purposes of this amendment are following: • To provide a detail breakdown for study duration, including approximately 1.5 years for recruitment. • To revise the exclusion criteria from HCV-RNA to HCV-Ab. The rationales are as below: i) Among the patients with positive HCV antibody, about 60% patients will be HCV-RNA. It is appropriate to use HCV antibody as a stricter exclusion

Document	Date of Issue	Summary of Change
		criteria, because most HCV-Ab positive patients are previously HCV infected or during chronic HCV infection. ii) Among the Chinese population, about 1% is HCV-Ab positive. Compared with HCV-RNA positive exclusion, HCV-Ab exclusion will not exclude much more patients. iii) HCV-RNA testing takes a comparably longer duration and has a high false negative rate. • To make any typographical edits, format updates and clarifications identified within and throughout the protocol.
Revised Protocol 01	03-Jan-2014	Incorporates Amendment 01
Amendment 01	03-Jan-2014	The purposes of this amendment are the following: • i) to include a multi-tumor Phase 1/2 study that serves as a Phase 1 study for both NSCLC and other indications with high priority in China; (ii) Detecting preliminary efficacy signal of nivolumab in specific tumor types to guide and accelerate the development in other tumor types in China. • Nivolumab has demonstrated clinical activity across a variety of solid tumors from completed Phase 1 studies at multiple tumor types, and ongoing studies in NSCLC, Melanoma and renal cancer. Also the pharmacokinetic and safety profile are similar across various solid tumor types. Patients with metastatic and refractory solid tumors represent a large population who have unmet medical needs in China. Despite advances in multimodal therapy, improvement in overall survival has been limited. The solid tumor types given priority consideration by China FDA for development include gastric cancer, esophageal cancer, and nasopharyngeal cancer. Thus this China phase 1/2 amendment will add 36 subjects with these 3 tumor types. • In the Section 1.1.1 study rationale, there is a comprehensive summary of nivolumab efficacy in a variety of tumors. The Section 1.4.4.3 anti-tumor activity summary is repeated and therefore is deleted. • The Section 1.5 risk/benefit assessment is revised for two considerations: i), instead of focusing only on NSCLC, there is general description of nivolumab efficacy in advanced solid tumors. ii), briefly explaining the mechanism of adverse events associated with nivolumab and management guideline. • To make any typographical edits, format updates and clarifications identified within and throughout the protocol.
Original Protocol	04-Mar-2013	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 06:

Nivolumab monotherapy 480mg Q4W flat dose is approved in melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of head and neck cancer, urothelial carcinoma and hepatocellular carcinoma by the FDA, and approved in melanoma and renal cell carcinoma by the EMA. To provide intensive PK data in multiple tumor types in Chinese subjects, the target study population in cohort D will change from "nasopharyngeal carcinoma" to "solid tumors".

[redacted]

Sample size will change from 12 subjects to up to 12 subjects in cohorts C and D to allow flexibility in study design.

This amendment applies to all enrolled subjects in cohort D.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis Section 3.1.2 Cohort Expansion Phase	Target study population in cohort D changed from "nasopharyngeal carcinoma" to "solid tumors".	To provide intense PK data in multiple tumor types.
Synopsis Section 3.1.2 Cohort Expansion Phase	Sample size changed from 12 subjects to up to 12 subjects in cohorts C and D.	To allow flexibility in study design.
Section 3.3.2 Exclusion Criteria Section 3.4.1 Prohibited and/or Restricted Treatments	2. Medical History and Concurrent Diseases has been updated. Live / attenuated vaccine within 30 days of first treatment is excluded, and minor updates in other exclusion criteria.	Investigator Brochure version 17 updates.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

SYNOPSIS

Clinical Protocol CA209077

CheckMate 077: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 077

Protocol Title: A Phase 1/2, Open-Label Study of Nivolumab (BMS-936558) in Chinese Subjects with Previously Treated Advanced or Recurrent Solid Tumors

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):
In the Dose Evaluation Phase, nivolumab (3mg/kg) will be administered as a single intravenous infusion (IV) over 60 minutes every 14 days for a total of 4 infusions in each cycle.
In the Cohort Expansion Phase,

- Nivolumab administered IV over 30 minutes at 3 mg/kg every 14 days for a total of 4 infusions in each cycle.

or

- Nivolumab administered IV over 30 minutes at 240 mg (flat dose) every 14 days for a total of 4 infusions in each cycle.

or

- Nivolumab administered IV over 30 minutes at 360 mg (flat dose) every 3 weeks

or

- Nivolumab administered IV over 30 minutes at 480 mg (flat dose) every 4 weeks

Subjects will receive nivolumab treatment until disease progression, intolerable toxicities, withdrawal of consent, or the study ends.

Study Phase: 1/2

Research Hypothesis: There is no formal primary research hypothesis for this study to be statistically tested.

Objectives:

Primary Objectives: To characterize the safety, tolerability, and dose limiting-toxicities (DLTs) of nivolumab in Chinese subjects with previously treated advanced or recurrent solid tumors.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of nivolumab in Chinese subjects;
- To assess the immunogenicity of nivolumab in Chinese subjects;
- To assess preliminary anti-tumor activity of nivolumab in Chinese subjects.

[redacted]

Study Design: This is a Phase 1/2 open-label study of nivolumab monotherapy in Chinese subjects with previously treated advanced or recurrent solid tumors. Nivolumab is a fully human monoclonal IgG4 antibody, targeting the programmed death-1 (PD-1) membrane receptor on T-lymphocytes and other cells of the immune system.

The study will consist of 3 periods: screening period (up to 28 days); treatment period (until disease progression or intolerable toxicities); and a follow-up period (up to 100 days). In the dose evaluation phase, each treatment cycle is comprised of 4 doses of assigned study drug (see table below) administered at Days 1, 15, 29 and 43 with a response assessment between Days 49 to 56. The response assessment must be completed before the first dose in the next cycle. In cohort expansion phase, the 3 mg/kg and 240 mg Q2W cohorts (cohort A and B) will be administered 4 doses in each 8-week treatment cycle, the same as the dose evaluation treatment cycle. The response assessment

must be completed before the first dose in the next cycle. The 360 mg Q3W cohort (cohort C) will be administered one dose of study drug in each 3-week treatment cycle. Tumor assessment must be completed every 6 weeks. The 480 mg Q4W cohort (cohort D) will be administered one doses of study drug in each 4-week treatment cycle. Tumor assessment must be completed every 8 weeks.

Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit.

Nivolumab Dose Levels

Nivolumab Dose Level in Dose Evaluation Phase	**Dose**
1	3 mg/kg
-1[a]	1 mg/kg
Nivolumab Dose Level in Cohort Expansion Phase	**Dose**
3 mg/kg Q2W	3 mg/kg
240 mg Q2W	240 mg
360 mg Q3W	360 mg
480 mg Q4W	480 mg

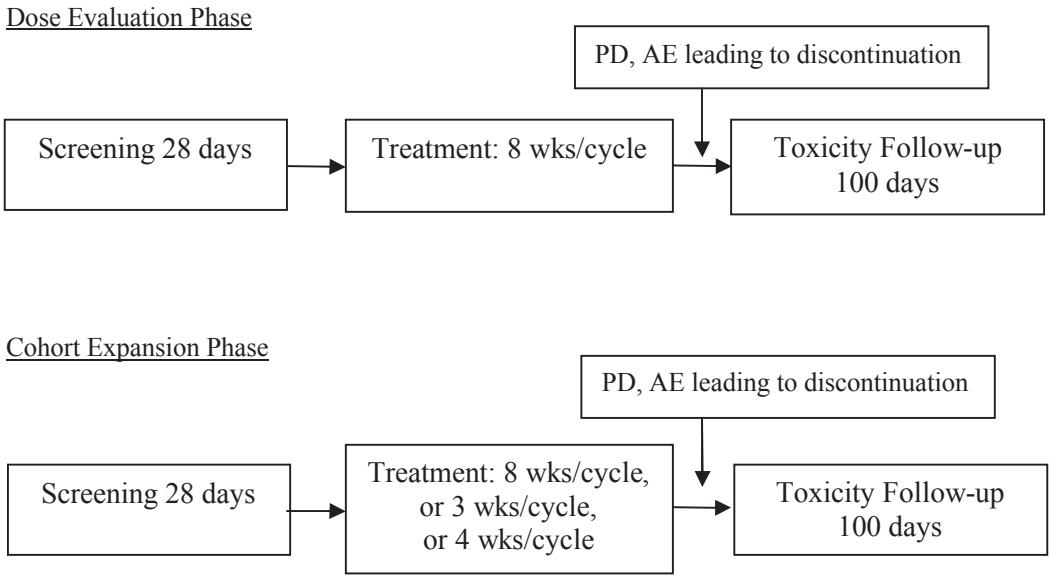
[a] Dose level -1 will only be considered if the safety and tolerability profile for 3 mg/kg is evaluated as not acceptable.

In 3mg/kg cohort and 240mg Q2W cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 3/Day 1 and will remain in the clinical facility until 24 hours after study drug administration. In 360mg Q3W Cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 6/Day 1 and will remain in the clinical facility until 24 hours after study drug administration. In 480mg Q4W Cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 5/Day 1 and will remain in the clinical facility until 24 hours after study drug administration.

Collection of tumor tissue [archival or recent acquisition, formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides] for determination of PD-L1 expression status is highly encouraged. Recent biopsy tissue is preferred when available. Submission of archival tissue is also encouraged for all subjects, irrespective of whether recent biopsy tissue is available. This is not applicable to cohort D

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times (see Time and Events Schedule Table 5.1-1, Table 5.1-2, Table 5.1-3 and Table 5.1-4) throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study.

Study Design Schematic



PD= progressive disease; AE= adverse event

Dose Evaluation Phase

Based on clinical experience with over 300 subjects on up to 2 years of treatment (study CA209003/MDX1106-03), the recommended dose of nivolumab during the dose evaluation phase of the study is 3 mg/kg. Dose limiting toxicity (DLT) observation period for each subject is defined as the 1st cycle of treatment (56 days of dosing). Initially 6 eligible NSCLC subjects will be treated at the dose level of 3 mg/kg. An additional 3 NSCLC subjects may be added to the same dose level, and hence a total number of 6 or 9 subjects will be treated during the dose evaluation phase for a given dose level. A decision to enter cohort expansion phase, or to consider the next lower dose level (1 mg/kg) in dose evaluation phase, will be guided by the number of subjects with DLTs observed during the dose evaluation phase (see table below).

Subjects who do not complete the DLT observation period for reasons other than DLTs will be replaced. A dose level of 1 mg/kg may be considered if the safety and tolerability profile for 3 mg/kg is evaluated as not acceptable, after consultation and agreement between the Investigator(s) and the sponsor as well as review of the existing clinical safety database from earlier studies. Following a similar procedure, if the dose level of 1 mg/kg is evaluated as not acceptable as well, the findings will be discussed between the Investigator(s) and the sponsor and an agreement will be reached as to whether a lower dose of nivolumab should be examined.

Safety monitoring during the dose evaluation phase will be based on the probability of the toxicity given the observed DLTs, with target toxicity of 0.25 (± 0.05). (Ji et al. *Clinical Trials* 2010; 7: 653–663, A modified toxicity probability interval method for dose-finding trials). Guidance for safety monitoring after the toxicity outcomes observed is presented in the following table:

Guidance for Safety Monitoring Based on Observed Toxicity Outcomes during the Dose Evaluation Phase

		Number of Subjects Treated	
		6	**9**
Number of Subjects with DLTs	**0**	E	E
	1	S	E
	2	S	E
	3	D	E
	4	NA	D

E: Expand to 56 - 64 subjects; **S**: Stay at the same dose level by treating additional 3 subjects; **D**: Discuss of proceeding with the next lower dose level.

Cohort Expansion Phase

If the safety and tolerability profile is established at the dose level of 3 mg/kg in the dose evaluation phase, then cohort expansion phase will be initiated, including:

- Cohort A: Continue to accrue up to at least 12 - 20 subjects with solid tumors (including but not limited to NSCLC) at the dose level of 3 mg/kg;
- Cohort B: Accrue 20 subjects with solid tumors (including but not limited to HCC, SCLC) at the dose level of 240 mg (flat dose) Q2W;
- Cohort C: Accrue up to 12 subjects with solid tumors (including but not limited to GC, NSCLC) at 360 mg (flat dose) Q3W;
- Cohort D: Accrue up to 12 subjects with solid tumors at 480 mg (flat dose) Q4W

Clinical safety monitoring of subjects during the cohort expansion phase will be performed. If in a given dose level, the combined incidence exceeds 33% for study drug related toxicity requiring treatment discontinuation, then further enrollment to that dose level will be interrupted and a decision whether or not to continue dosing will be based on discussions of the observed aggregate (acute and chronic) toxicities between the Investigator(s) and the sponsor, if needed. An agreement will be reached as to whether a lower dose should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects to that arm. Depending on preliminary efficacy data, certain tumor types may be expanded to collect additional efficacy data.

Administration of Additional Cycles:

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumor (RECIST v1.1). In 3 mg/kg cohort and 240mg Q2W cohort, end of cycle tumor response assessment for all subjects will occur between Days 49 to 56 (results of the assessments must be reviewed and documented before the first dose of next cycle). In 360 mg Q3W cohort, tumor assessment must be completed every 6 weeks. In 480 mg Q4W cohort, tumor assessment must be completed every 8 weeks.

Subjects will continue to receive nivolumab treatment until disease progression (or until discontinuation of study therapy in subjects receiving nivolumab beyond progression, defined in Section 4.3.2.5), discontinuation due to toxicity, or withdrawal of consent. The maximum duration of study therapy to be administered to an individual subject in this study is 2 years.

Follow-up Period:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with nivolumab);
- The first two follow-up visits (follow up #1 and follow up #2) include PK and immunogenicity samples. Follow up #1 = 30 days from last dose ± 5 days; Follow up #2 = 70 days from follow up #1 ± 5 days;
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible.

Duration of Study: The expected maximum duration of a subject's participation in the study (on-treatment and follow-up periods) is approximately 2.5 years. The study is expected to accrue over a period of approximately 1.5 years.

- maximum 28 days of screening,
- Maximum of 2 years of therapy.
- approximately 100 days follow-up office visits.

Number of Subjects: approximately 56 - 64 PK evaluable subjects.

Study Population: Male and female subjects, 18 years of age or older, who have histological confirmation of solid tumor that is clinically advanced or recurrent, and have progressed after previous therapies, and for whom no alternative standard therapy is available will be eligible to enroll in the study:

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 first dose.

Study Assessments:

- **Safety Assessment:** Safety assessments will be based on the following: clinical laboratory tests, pregnancy testing, Eastern Cooperative Oncology Group (ECOG) status, physical examination including vital signs and electrocardiogram (ECG), and adverse events (AEs). Toxicity will be evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03;
- **Dose-Limiting Toxicity:** DLTs are defined in protocol Section 4.3.1 and will be determined based on the incidence, intensity, and duration of adverse event (AE) that are related to study drug, and that occur within 56 days (8 weeks, through completion of cycle 1) of initiation of study drug;
- **Immunogenicity Assessment:** Blood samples to evaluate development of positive anti-drug antibody (ADA) response will be collected at specified time points for all subjects;
- **Pharmacokinetics Assessment:** Serial blood samples for PK assessments will be collected from all subjects at specified time points. PK samples will also be collected to evaluate serum concentrations of nivolumab at follow-up visits. PK parameters such as Cmax, Tmax, AUC(TAU), Ctrough, and Accumulation Index (AI) will be derived from serum concentration versus time data in all subjects.
- **Efficacy Assessment**: Computed tomography/magnetic resonance imaging (CT/MRI) for chest, abdomen, pelvis, and brain will be performed at screening and at specified time points in Table 5.1-2, Table 5.1-3 and Table 5.1-4.. Measurement of tumor burden must be reviewed and documented before initiating further treatment with nivolumab. Tumor response status will be assessed with RECIST v1.1;
- [redacted]

Statistical Considerations:

Sample Size: This is a Phase 1/2 safety trial and the sample size during the dose evaluation phase depends on the observed toxicity. Six or 9 NSCLC subjects per dose level will be treated according to the Guidance for Safety Monitoring Based on Observed Toxicity Outcomes during the Dose Evaluation Phase. Utilizing the information on the observed toxicity of related AEs with Grades 3 and 4 (16%) among 304 subjects in a multidose, dose-ascending study with nivolumab monotherapy in subjects with selected advanced or recurrent malignancies (CA209003/MDX1106-03), there is a less than 20% posterior probability with this guidance that the toxicity rate could be 40% or higher, for different total number of subjects (6 or 9) in the dose evaluation phase. The posterior probability calculations assume a Beta(1, 4) prior distribution, which implies a toxicity rate around 20% as estimated from CA209003/MDX1106-03 study. Similarly, there is a less than 10% posterior probabilities that the toxicity rate could be 45% or higher for the dose evaluation phase.

One of the objectives of expansion cohorts is to characterize the pharmacokinetics (PK) of nivolumab in Chinese subjects in different dosing regimens. The sample size of 12-20 in the expansion cohorts is adequate to characterize PK within a dosing group.

Approximately 6-9 subjects are expected to be enrolled in dose evaluation and to be expanded to approximately 56-64 in total.

Endpoints:

Primary endpoints

The primary objective is to characterize the safety and tolerability of nivolumab in Chinese subjects. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.03 (as assessed at the planned times listed in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

Secondary endpoints

The secondary objective of characterizing the PK of nivolumab in Chinese subjects will be measured by:

- Nivolumab PK parameters, including Cmax, Tmax, AUC(TAU), Ctrough, CLT, T-HALFeff and AI.

The secondary objective of assessing the immunogenicity of nivolumab will be measured by:

- Frequency of ADA positive status and ADA negative status, relative to baseline.

The secondary objective of assessing the anti-tumor response of nivolumab will be measured by the following efficacy endpoints at subject level:

- BOR by investigator using Response Evaluation Criteria in Solid Tumor (RECIST v1.1);
- Duration of response is computed for subjects with a best overall response (BOR) of CR or PR, and defined as the time between the date of first response and the subsequent date of objectively documented disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment;

The following efficacy endpoints for each tumor type may be assessed by dose and/or across dose depending on data availability.

- Objective response rate (ORR) is defined as the proportion of all treated subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) by investigator using Response Evaluation Criteria in Solid Tumor (RECIST v1.1);
- Median duration of response
- Response rate at 24 weeks: is defined as the proportion of all treated subjects who has CR or PR by 24 weeks.
- Disease control rate (DCR) at 24 weeks is defined as the proportion of all treated subjects who has CR, PR or SD by 24 weeks

Analyses:

Safety analysis

All recorded AEs will be coded according to the most current version of MedDRA and listed by dose level and tumor type and overall. AEs will be summarized for each dose level and tumor type and overall by system organ class and preferred term using the worst grade within each category within a subject. Toxicity changes from baseline in clinical laboratory test results will be summarized by dose level and tumor type and overall using the worst on-treatment CTC grade values. Vital signs, ECGs and clinical laboratory test results will be listed and summarized by dose level and tumor type and overall.

Efficacy analysis

Individual subject's BOR will be listed by dose and/or across dose if appropriate for each tumor type based on RECIST v1.1. BOR outcomes will be tabulated, by dose and/or across dose if appropriate, for each tumor type depending on data availability.

Individual subject's DOR will be listed by dose and/or across dose if appropriate for each tumor type.
The following analysis for each tumor type may be summarized by dose and/or across dose depending on data availability.
ORR will be calculated and corresponding two-sided 95% exact confidence intervals using Clopper and Pearson method will be provided by dose and/or across dose for each tumor type depending on data availability.
Response rate and disease control rate at 24 weeks will be estimated by Kaplan-Meier analysis of time to response and the corresponding two-sided 95% confidence interval by Greenwood formula will be provided by dose and /or across dose for each tumor type as appropriate.

Median duration of response will be estimated by Kaplan-Meier analysis and corresponding two-sided 95% confidence intervals by Greenwood formula will be provided by dose and/or across dose for each tumor type as appropriate.

Pharmacokinetic analysis

Summary statistics will be tabulated for PK parameters of nivolumab as specified in Section 5.5. by dose and study cycle as appropriate.

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development programs to develop or refine a population PK model in a separate report.

Immunogenicity analysis

Data from the assessment of immunogenicity markers will be listed by subjects. Number and frequency of ADA response classifications will be summarized by dose level. The details of the ADA response classifications will be provided in the study statistical analyses plan (SAP) document. Effect of immunogenicity on safety/efficacy [redacted] and PK may be explored.

[redacted]

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

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. Many tumors express tumor-specific antigens and ongoing immune surveillance may abort the emergency of many tumors as they arise. Meanwhile, tumor progression may depend upon acquisition of mechanisms that allow cancer cells to evade immune surveillance and an effective immune response.[1]

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 - either indirectly by cytokine manipulation or directly by stimulation of immune cells by antibodies directed to receptors on T and B cells.

Unmet medical needs

Patients with metastatic or refractory solid tumors have very poor prognosis. Despite advances in multimodal therapy, improvement in overall survival has been limited. Thus, these patients represent a large population who have unmet medical needs and it is necessary to test compounds that have novel mechanisms of action in clinical studies.

In China, cancer is becoming the leading cause of death in urban area and the second one in rural area.[2, 3] There are certain tumor types given high priority consideration in China due to the high incidence rate, etiology, clinical characteristic and outcomes. These tumor types include lung, stomach, esophageal and nasopharyngeal cancer.

Lung cancer is the most common type of cancer in China and leading cause of cancer-related death globally and in China. The reported number of lung cancer cases in China in 2008 was 522,050 with an incidence of 33.5 per 100,000 age standardized rate (ASR).[4] The reported number of deaths in China from lung cancer for 2008 was 452,813. Approximately 80-85% of lung cancer patients have Non-Small-Cell Lung Cancer (NSCLC). The majority of patients present with locally advanced or distant metastatic disease that is not amenable to cure by surgery and/or radiotherapy, and therefore eligible for systemic treatment. Despite the availability of new agents, the prognosis for advanced NSCLC patients remains poor. Almost all patients eventually develop progressive disease.

Gastric cancer is the second highest malignancy in terms of incidence in China, and yearly new cases in China accounts for more than 40% of all the new gastric cancer cases in the world.[4] The prognosis of advanced gastric cancer patients is very poor with an overall survival of about 6 to 8 months.[5]

Esophageal cancer ranks as the fifth tumor for incidence rate in China, and new cases in China each year account for 50% of all new cases in the world.[4,6] The primary treatment regimens for esophageal cancer in China are surgery and radiotherapy. For the advanced esophageal cancer

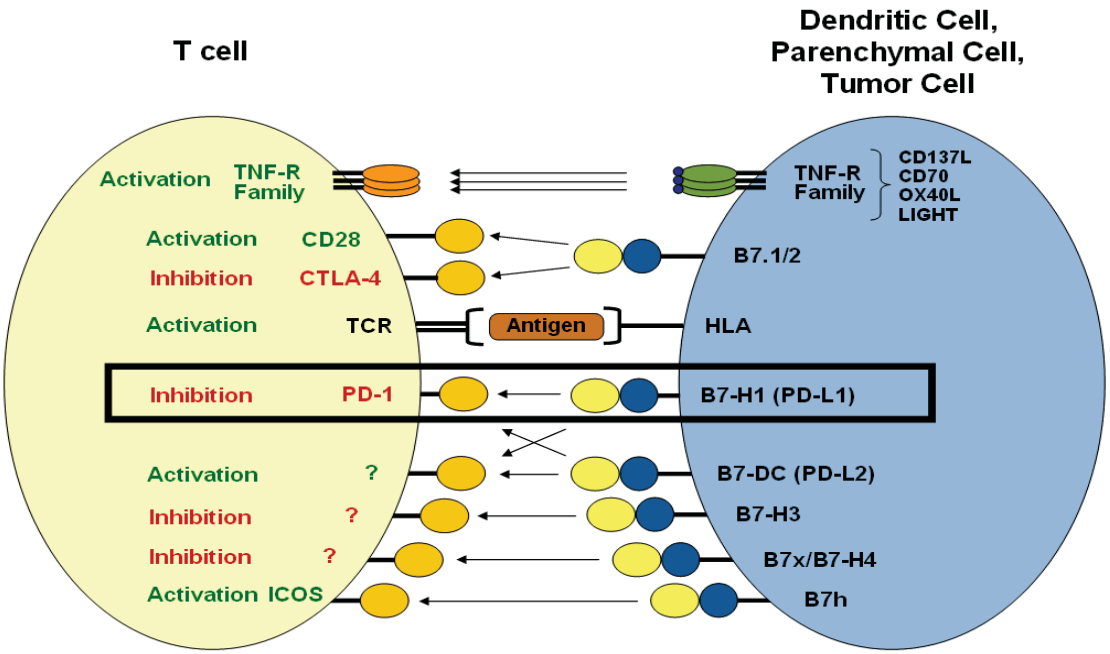
patients, the treatment options are very limited and there is high unmet medical needs for this population.

Nasopharyngeal cancer (NPC) is a type of tumor distributed in specific regions and ethnic groups such as the Asians. About 80% of nasopharyngeal cancer patients come from Asia with China accounting for about 40% for all new cases worldwide yearly.[6,7] Nasopharyngeal cancer can be cured by radiotherapy if diagnosed at early stage. In China, 75% of newly diagnosed NPC are stage III or IV.[8] For recurrent, unresectable or metastatic nasopharyngeal cancer, the treatment options are very limited and the prognosis remains poor with TTP of 5 to 10 months and OS of 12 to 18 months. [9,10,11]

Nivolumab Mechanism of Action

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) Figure 1-1.[12] Collectively, these signals govern the balance between T cell activation and tolerance to antigens.

Figure 1-1: T cell Stimulation



Programmed death-1 (PD-1 or CD279), primarily expressed on activated T cells, B cells and myeloid cells, is a 55 kD type I transmembrane protein that is a member of the CD28 family of T cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[13] Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PDL2 (also known as B7-DC or CD273), each of which are primarily expressed on antigen presenting cells. PD-L1 and PD-L2 have been shown to downregulate T cell activation upon

binding to PD-1 in both murine and human systems.[14,15,16] The interaction of PD-1 with its ligands, PD-L1 and PD-L2 transmits a negative regulatory stimulus to down-modulate the activated T cell immune response.

The absence or inhibition of PD-1 in murine models has resulted in development of various autoimmune phenotypes or autoimmune diseases,[17] which suggests inhibition of PD-1 binding to its ligands has the potential to activate anti-self T cell.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. The effects of anti-PD-1 blockade in combination with a variety of chemotherapeutic agents were tested in several murine tumor models (MC38, SA1/N, and PAN02).

In humans, PD-L1 expression has been found in a number of tumors.[18,19] PD-L1 expression by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[20] Moreover, the expression of PD-L1 may protect tumor cells from the induction of apoptosis by activated tumor-specific T cells.[21] PD-1 expression has also been associated with poor prognosis in renal, esophageal, gastric, ovarian, pancreatic, and lung cancer.[22,23,24] PD-1 engagement on T cells by PD-L1+ APC or PD-L1 + tumor cells may prematurely limit the effective immune response.

Thus, blocking PD-1 in PD-L1+ tumors may reverse the inactivation of tumor-specific effector T cells as well as activate antitumor immune responses that are limited by expression of PD-L1 on adenomatous polyposis coli (APC) or tumor cells.

Nivolumab (also known as BMS-936558, MDX-1106, Ono-4538, anti-PD-1) is a fully human, IgG4 (kappa) isotype mAb, PD-1 receptor blocker. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and interferon (IFN)-γ release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cell (PBMC), and was evaluated by enzyme-linked immunosorbent assay (ELISA). These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner. PD-1 blockade by nivolumab has, therefore, been pursued as a promising avenue for immunotherapy of tumors.

1.1 Study Rationale

Nivolumab has demonstrated clinical activity in a variety of solid tumor malignancies from completed and ongoing studies. Patients with metastatic and refractory solid tumors represent a large population who have unmet medical needs in China and throughout the world. Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, and some lymphomas. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC and in subjects with unresectable or metastatic melanoma. The

overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date. The most common adverse events were inflammatory, consistent with its mechanism of action, and were generally manageable. These safety data were established in a population predominantly by Caucasian subjects; therefore, the safety, tolerability and pharmacokinetics of nivolumab will be assessed in Chinese subjects with advanced solid tumors, to provide a more comprehensive understanding of nivolumab's properties in Chinese.

1.1.1 Rationale for Nivolumab as Monotherapy in Advanced Solid Tumors

CA209003/MDX1106-03 is a completed Ph1 study of Nivolumab monotherapy in selected advanced malignancies. A total 306 subjects were treated with Nivolumab monotherapy, including 129 NSCLC, 107 melanoma, 34 RCC, 17 CRPC and 19 CRC patients. The objective, durable responses were observed in subjects with NSCLC, melanoma, and RCC (see Table 1.1.1-1 from CA209003/MDX1106-03 CSR[25]). Responses were even observed in subjects who were heavily pretreated (nearly half had received ≥ 3 prior therapies). The observed responses were durable with a median duration of response (DOR) ranging from 56 -104 weeks across tumor types. An analysis of PFSR in all treated NSCLC, melanoma and RCC subjects showed a 24-week rate of 33%, 45% and 58% respectively. An analysis of OS in all treated NSCLC, melanoma and RCC subjects showed 1-year rate of 42%, 62% and 70%.

Table 1.1.1-1: Summary of Efficacy - All Treated Subjects with Non-small Cell Lung Cancer (NSCLC), Melanoma, or Renal Cell Carcinoma (RCC)

Efficacy parameter	SQ NSCLC n = 54	NSQ NSCLC n = 74	TOTAL NSCLC N = 129	Melanoma N = 107	RCC N = 34
Best Overall Response (BOR) [a], N (%)					
Complete Response	0	0	0	1(0.9)	1(2.9)
Partial Response	9 (16.7)	13 (17.6)	22 (17.1)	32 (29.9)	9 (26.5)
Stable Disease	15 (27.8)	16 (21.6)	32 (24.8)	24 (22.4)	14 (41.2)
Disease Progression	20 (37)	38 (51.4)	58 (45.0)	41 (38.3)	8 (23.5)
Unable to Determined	10 (18.5)	7 (9.5)	17 (13.2)	9 (8.4)	2 (5.9)
Objective response rate (ORR)[b], N (%)	9 (16.7)	13 (17.6)	22 (17.1)	33 (30.8)	10 (29.4)
95% CI	7.9, 29.3	9.7, 28.2	11.0, 24.7	22.3, 40.5	15.1, 47.5
Time to response (range, weeks)	7.4 - 15.4	7.6 - 31.4	7.4 - 31.4	7.1 - 40.0	7.7 - 47.7
Median DOR (weeks)	NR	63.9	74.0	104	56.1
95% CI from K-M	42.1, -	29, -	42.1, -	73.9, -	49.4, -
PFSR (95% CI)					

Table 1.1.1-1: Summary of Efficacy - All Treated Subjects with Non-small Cell Lung Cancer (NSCLC), Melanoma, or Renal Cell Carcinoma (RCC)

Efficacy parameter	SQ NSCLC n = 54	NSQ NSCLC n = 74	TOTAL NSCLC N = 129	Melanoma N = 107	RCC N = 34
At 8 weeks	94 (87, 100)	90 (83, 97)	92 (87, 97)	90 (85, 96)	100 (NC)
At 24 weeks	42 (27, 57)	29 (18, 39)	33 (25, 42)	45 (35, 55)	73 (58, 88)

[a] BOR was derived centrally by the sponsor using RECIST 1.0 criteria on investigator assessed tumor measurements.

[b] Includes all subjects with a response of CR or PR.

Source: Supplemental Tables S.5.1.1A, S.5.1.2, S.5.1.3, S.5.2.2A.
Abbreviations: CI: confidence interval, CR: complete response, DOR: duration of response, NR: not reached, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PR: partial response, SD: stable disease

Nivolumab monotherapy has demonstrated to have significant survival benefit with a more favorable safety profile compared to docetaxel in 2 recently completed Phase III NSCLC second-line studies (CA209017 for squamous NSCLC and CA209057 for non squamous NSCLC).[26]

Table 5.4.1.1-1: Summary of Key Efficacy Results - All Randomized Subjects in CA209057 and CA209017

	CA209057 (NSQ NSLC)		CA209017 (SQ NSCLC)	
Efficacy Parameter	Nivolumab N=292	Docetaxel N=290	Nivolumab N=135	Docetaxel N=137
PRIMARY ENDPOINT				
Overall Survival				
Hazard Ratio[a]	0.73 (0.59, 0.89)[b]		0.59 (0.43, 0.81)[c]	
Median (95% CI) (Months)[d]	12.2 (9.7, 15.0)	9.4 (8.1, 10.7)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Rate at 12 Months (95% CI)	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)
SECONDARY ENDPOINTS				
Objective Response Rate				
n (%)	56 (19.2)	36 (12.4)	27 (20.0)	12 (8.8)
95% CI[e]	(14.8, 24.2)	(8.8, 16.8)	(13.6, 27.7)	(4.6, 14.8)
Progression-free Survival				
Hazard Ratio (95% CI)[a]	0.92 (0.77, 1.11)		0.62 (0.47, 0.81)	
Median (95% CI) (Months)[d]	2.3 (2.2, 3.3)	4.2 (3.5, 4.9)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)
Rate at 12 Months (95% CI)	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)

These data suggested that nivolumab monotherapy induced substantial durable disease control in (heavily) pretreated subjects with advanced solid tumors. Thus, the study design and target population in this Phase 1 trial is to determine the safety, tolerability and pharmacokinetics of nivolumab monotherapy in Chinese subjects with advanced or recurrent solid tumors.

1.1.2 Rationale for schedule and dose selection in dose evaluation phase

In CA209003/MDX1106-03 study, nivolumab was administered every 2 weeks at doses of 0.1, 0.3, 1, 3 and 10 mg/kg. For melanoma and RCC, there was no apparent dose-response effect, whereas in NSCLC, nivolumab at ≥ 3mg/kg yielded greater responses than at 1mg/kg. The data

indicates that anti-tumor activity observed in NSCLC appeared to approach a plateau (see Table 1.1.2-1). 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 and 10 mg/kg administered every 2 weeks.

Table 1.1.2-1: Objective Response Rate per RECIST 1.0 and Progression Free Survival 24 Weeks Rate by Histology in Non-small Cell Lung Cancer Subjects - MDX1106-03

Dose (mg/kg)	N	Histology	ORR No. of Subjects (%)	95% CI of ORR	PFSR at 24 weeks (%)	95% CI of PFSR
All NSCLC	**129**	**NA**	**22(17)**	**11 - 25**	**34**	**25 - 42**
1.0	15	SQ	0	0	36	11-61
	18	NSQ	1(6)	0.1 - 27	19	0-39
3.0	18	SQ	4(22)	6-48	45	21-70
	19	NSQ	5(26)	9-51	42	20-64
10.0	21	SQ	5(24)	8-47	45	23-67
	37	NSQ	7(19)	8-35	25	11-39

Abbreviations: CI: confidence interval, NA: not applicable, NOS: not otherwise specified; NSCLC: non-small cell lung cancer; NSQ: non-squamous, ORR: objective response rate; PFSR: progression free survival rate, SQ: squamous
Source: Preliminary data, MDX1106-03. Clinical cut-off date 18-Mar-2013.

Also, the safety profile of nivolumab as a single agent is consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10mg/kg. There is no apparent dose-related toxicity pattern in terms of incidence, severity and drug-related AEs and drug-related SAEs. Please refer to the most current version of the BMS-936558 Investigators Brochure (IB).

[redacted]

Based on the safety and anti-tumor activity in western and Japanese subjects, nivolumab will be administered every 2 weeks with a starting dose of 3 mg/kg in Study CA209077.

1.1.3 Rational for flat dose in cohort expansion phase

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation in nivolumab global program.

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used. PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a

dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate 100 virtual trials, each consisting of two arms, nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer patients. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to patients with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W. In the range of 50 to 70 kg, the exposures following 240 mg Q2W are predicted to be approximately 16.8% greater for those subjects in comparison to the 3 mg/kg, 80 kg reference group. Two more flat dosing regimens, nivolumab 360 mg Q3W and 480 mg Q4W, will be investigated in this protocol to further explore a convenient dosing regimen for nivolumab monotherapy and in combination with other therapies. As the PK of nivolumab is linear, 360 mg Q3W and 480 mg Q4W dosing regimens are predicted to provide Cavgss similar to 3 mg/kg or 240 mg Q2W. However, these two regimens are expected to result in higher Cmax (up to approximately 20%), and lower Cminss (up to approximately 10%) compared to 3 mg/kg Q2W. Given that nivolumab was adequately tolerated up to 10 mg/kg, and the exposure-response relationship for safety is flat, a slight increase in Cmaxss is not expected to increase the safety risk of nivolumab. A marginal decrease in Cminss is also not expected to reduce the efficacy as high trough concentrations and > 90% PD-1 receptor occupancy are still maintained. Thus, Nivolumab 360 mg Q3W and 480 mg Q4W are expected to have similar efficacy and safety profile to nivolumab 3 mg/kg Q2W, and these two regimens are currently under investigation in nivolumab program as well.

1.1.4 Rationale for Shorter Infusion Times

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

Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were grade 1-2 and were manageable. Assuming ~60kg body weight on average in

Chinese subjects, therefore, 240mg (~4mg/kg), 360(~6mg/kg), 480(~8mg/kg) would be all within the exposure range of 10mg/kg (safe up to 20mg/kg in Japan ph1), thus additional safety concern is not expected. Preliminary analysis from CA209153 demonstrated that nivolumab 3 mg/kg can be safely infused over 30 min. The safety profile of 30 min infusion (N=322) is comparable to that of 60 min infusion (N=355), with a similar incidence of infusion-related reactions (3% vs. 2%, respectively). Grade 3/4 reactions were rare (less 1% for both) in both cases. Therefore, an infusion duration of 30 minutes for 3 mg/kg, 240 mg, 360 mg, and 480 mg is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

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

1.1.5 Rationale for Nivolumab Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease.[27] This phenomenon was observed in approximately 10% of subjects in the Phase I 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 which would appear as enlarged index lesions and as new lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of radiographic improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become radiographic apparent. Therefore subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.3.2.5). Such subjects must discontinue study therapy upon evidence of further progression in subsequent radiographic evaluation.

1.2 Research Hypothesis

There is no formal primary research hypothesis for this study to be statistically tested.

1.3 Objectives

1.3.1 Primary Objective

To characterize the safety, tolerability, and dose limiting-toxicities (DLTs) of nivolumab in Chinese subjects with previously treated advanced or recurrent solid tumors.

1.3.2 Secondary Objectives

- To characterize the pharmacokinetics (PK) of nivolumab in Chinese subjects;
- To assess the immunogenicity of nivolumab in Chinese subjects;
- To assess preliminary anti-tumor activity of nivolumab in Chinese subjects.

[redacted]

1.4 Product Development Background

1.4.1 Pharmacology

The ability of nivolumab to bind to PD-1 was determined using Biacore and ELISA as well as FACS and Scatchard analysis to PD-1+ transfectants and activated T cells. Nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibit the binding of PD-1 to its ligands PD-L1 and PD-L2. Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA.

Nivolumab was shown to promote the proliferation of human T cells in a variety of assays.

Detailed information can be found in the current version of the BMS-936558 IB.

1.4.2 Toxicity

Detailed information can be found in the current version of the BMS-936558 IB.

1.4.3 Preclinical Metabolism and Pharmacokinetics

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of mAbs is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

The apparent elimination half-life (T-HALF) of nivolumab at 1 mg/kg in Cynomolgus monkey estimates was 124 to 139 hours. The T-HALF estimate at 10 mg/kg for was 261 hours, but the data were variable (SD=200 hours). Consistent with the long T-HALF, total serum clearance was low. Systemic exposure to nivolumab increased in an approximately dose-proportional manner.

Detailed information can be found in the current version of the BMS-936558 IB.

1.4.4 Clinical Pharmacology and Safety

1.4.4.1 Pharmacokinetics of Nivolumab

Single dose PK of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple doses PK were being evaluated in subjects in CA209003/MDX1106-03. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from about 350 subjects from MDX1106-01, MDX1106-02, and CA209003/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 (i.e., 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 current version of the IB.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003/MDX1106-03. 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.

1.4.4.2 Safety Summary

CA209003/MDX1106-03 was a Phase 1 multi-dose escalation study in subjects with previously treated advanced or metastatic melanoma, RCC, NSCLC, colorectal cancer, or hormone-refractory prostate cancer. In CA209003/MDX1106-03, subjects were administered nivolumab intravenously every 2 weeks with doses of 0.1, 0.3, 1, 3, or 10 mg/kg.

No MTD was identified in CA209003/MDX1106-03. The maximum dose level evaluated was 10 mg/kg. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types.

As of the clinical cut-off date (3-July-2012), 296 (97.4%) out of 304 subjects treated by nivolumab had at least 1 reported AE regardless of causality. There was no pattern in the incidence, severity or relationship of AEs to the nivolumab dose level. Treatment-related AEs of any grade occurred in 220 (72.4%) of subjects. The most frequent drug-related AEs occurring in ≥ 5% of subjects included: fatigue (25.7%), rash (13.5%), diarrhea (11.8%), pruritus (10.2%), nausea (7.9%), decreased appetite (7.9%), hemoglobin decreased (5.9%) and pyrexia (5.3%). Most treatment related AEs were low grade (Grade 1-2). Treatment related high-grade (Grade 3-4) AEs were reported in 45 (14.8%) of subjects, with the most common being fatigue (1.6%), decreased appetite (1.0%) and diarrhea (1.0%). At least one SAE was reported for 150 (49.3%) of the 304 subjects at all dose levels. Grade 3-4 SAEs were reported for 23 subjects (7.6%). Drug-related serious adverse events (SAEs) occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included diarrhea: 3 subjects (1.0%), pneumonitis: 3 subjects (1.0%), pneumonia: 2 subjects (0.7%) and lipase increased: 2 subjects (0.7%). Similar to the overall AE profile, there was no apparent relationship in the incidence or severity of drug-related AEs to nivolumab dose level. There were no apparent differences in the frequency of AEs based on subjects' tumor type.

Additional select treatment-related AEs have occurred with low frequency (< 5%) but are considered clinically meaningful, as they require greater vigilance for early recognition and prompt intervention. These AEs include: alanine aminotransferase (ALT) increased (4.3%), aspartate aminotransferase (AST) increased (3.6%), pneumonitis (3.3%), hypothyroidism (3.0%), hyperthyroidism (1.3%), adrenal insufficiency (0.7%) and colitis (0.7%). Grade 3-4 events of pneumonitis were reported in 3 subjects (1.0%) as described above (1 event was Grade 4). Grade 3 events of colitis, ALT increased and AST increased were reported in 2 subjects (0.7%) each. Grade 3 events of adrenal insufficiency, hyperthyroidism and hypothyroidism were

reported in one subject (0.3%) each. Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, endocrinopathy and nephrotoxicity (Appendix 1). These algorithms are updated regularly and are, therefore, contained within the most recent version of the BMS-936558 IB.

Treatment-related AEs leading to discontinuation were reported in 18 (5.9%) of the 304 treated subjects on CA209003/MDX1106-03. The only events reported in more than one subject were pneumonitis: 4 subjects (1.3%) and hepatitis: 2 subjects (0.7%). There were 3 (1.0%) drug-related deaths; each occurred after the development of pneumonitis.

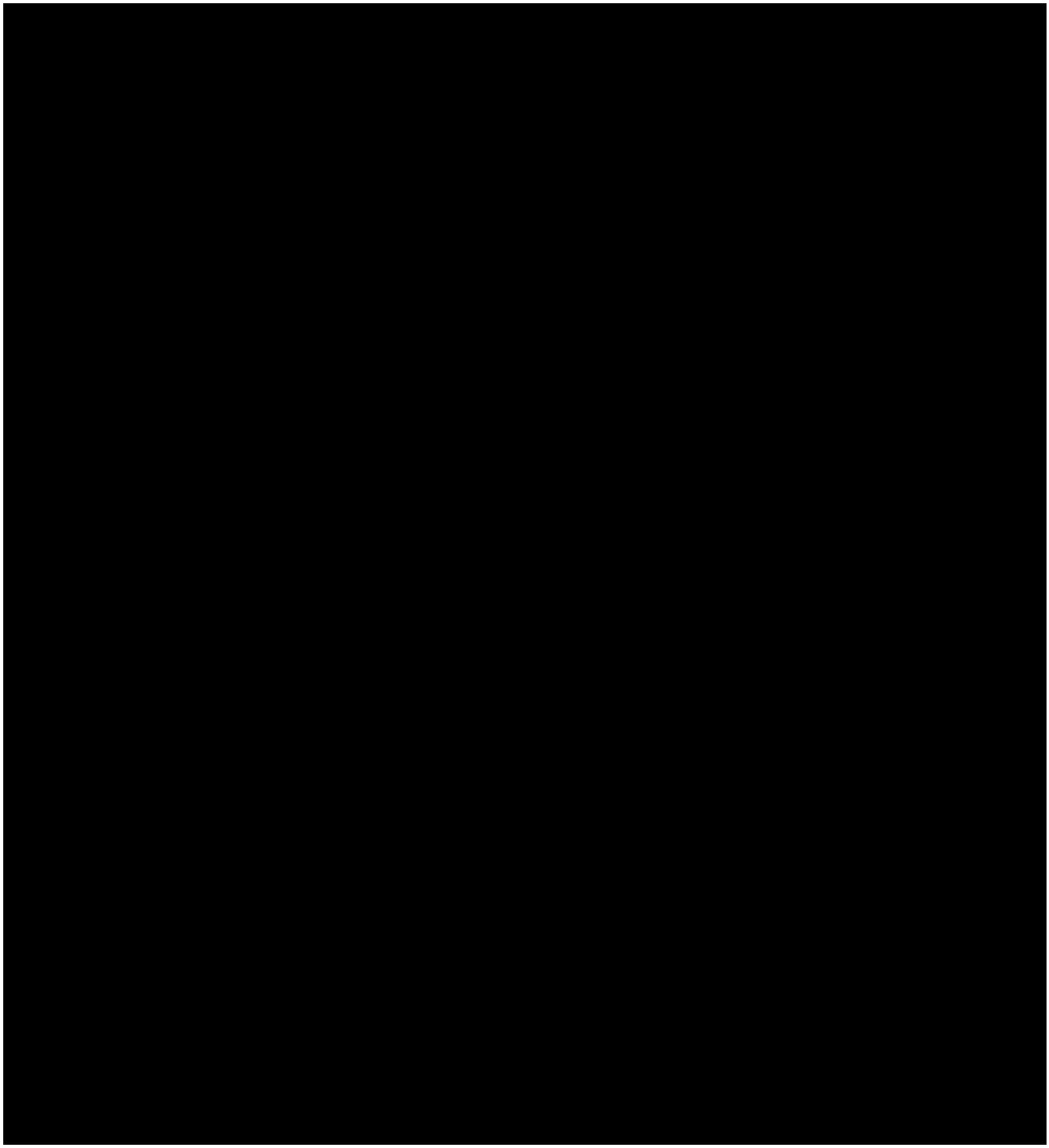
In CA209063 (Phase II single arm study with 117 squamous NSCLC patients failed at least 2 prior regimens), seventy-four percentages of patients reported a treatment-related adverse event of any grade; most commonly, fatigue (33%), decreased appetite (19%), and nausea (15%). Grade 3 ~ 4 treatment-related adverse events occurred in 20 of 117 (17%) of patients, most commonly fatigue (4%), pneumonitis (3%), and diarrhoea (3%). Most treatment-related immune mediated adverse events were of low grade, with skin disorders (15%) and gastrointestinal events (10%) most prevalent. Nivolumab has a manageable safety profile in previously treated advanced squamous NSCLC.[28]

In CA209017 (Phase III randomized study with 272 squamous NSCLC patients failed from one platinum doublet chemotherapy), treatment-related adverse events, including both hematologic and nonhematologic toxic events, occurred less frequently with nivolumab than with docetaxel. In the nivolumab group, 58% of the patients had events of any grade, 7% had events of Grade 3 or 4, and none had Grade 5 events; in the docetaxel group, 86% of the patients had events of any grade, 55% had events of Grade 3 or 4, and 2% had events of Grade 5. The most frequently reported treatment-related adverse events with nivolumab were fatigue (16%), decreased appetite (11%), and asthenia (10%); docetaxel-treated patients most frequently had neutropenia (33%), fatigue (33%), alopecia (22%), and nausea (23%). The most frequently reported (in □ 3% of patients) treatment-related select adverse events of any grade were hypothyroidism (4% with nivolumab vs. 0% with docetaxel), diarrhea (8% vs. 20%), pneumonitis (5% vs. 0%), increased blood creatinine level (3% vs. 2%), and rash (4% vs. 6%).[29]

In CA209057 (Phase III randomized study with 582 non-squamous NSCLC patients failed from one platinum doublet chemotherapy), the safety profile of nivolumab was favorable vs. docetaxel and consistent with prior studies. Grade 3~5 drug-related AEs occurred in 10.5% (30/287) of nivolumab and 53.7% (144/268) of docetaxel patients. No deaths were related to nivolumab vs 1 docetaxel-related death (due to grade 4 febrile neutropenia). The most frequently reported treatment-related adverse events of any grade with nivolumab were fatigue (16%), nausea (12%), decreased appetite (11%), and asthenia (10%). Docetaxel-related patients most frequently had neutropenia (31%), fatigue (29%), nausea (26%), alopecia (25%), and diarrhea (23%). The most frequently reported treatment-related select adverse events of any grade were hypothyroidism (7% with nivolumab vs. 0% with docetaxel), diarrhea (8% vs. 23%), ALT increased (3% vs. 1%), AST increased (3% vs. 1%), pneumonitis (3% vs. < 1%), and rash (9% vs. 3%).[30]

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[31] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are available in the most recent version of the BMS-936558 IB.



1.4.5 Clinical efficacy in Selected Tumor Types

Six clinical studies contributed to the clinical experience with nivolumab in subjects with NSCLC:

- CA209001 is a Phase I single-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 10 mg/kg with an option for re-treatment at 3 months.
- CA209003 is a Phase I/II open-label, multiple doses 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 data cutoff date (04-Feb-2013), 306 subjects were treated in CA209003, including 129 NSCLC subjects.
- CA209012 is a multi-arm Phase I safety study of nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab or as monotherapy in subjects with Stage IIIB/IV NSCLC.
- CA209063 is a Phase II single arm study in squamous NSCLC subjects (N = 117) who had failed from two or more previous treatments received nivolumab 3 mg/kg every 2 weeks.
- CA209017 is an open-label randomized Phase III study of nivolumab monotherapy (3 mg/kg) versus docetaxel for advanced squamous NSCLC patients with disease progression during or after one prior platinum doublet chemotherapy, 272 subjects were randomized.
- CA209057 is an open-label randomized Phase III study of nivolumab monotherapy (3 mg/kg) versus docetaxel for advanced non-squamous NSCLC patients with disease progression during or after one prior platinum doublet chemotherapy, 582 subjects were randomized.

In summary, Nivolumab has demonstrated durable responses as monotherapy in NSCLC. Nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in previously treated subjects with advanced or metastatic NSCLC.

Detailed information in other selected tumor types can be found in the current version of the BMS-936558 IB.

1.5 Overall Risk/Benefit Assessment

Patients with advanced or refractory solid tumors have great unmet medical need. Nivolumab monotherapy has encouraging anti-tumor activity (CR and PR) in Phase 1 studies in heavily pretreated advanced solid tumors (NSCLC, melanoma, RCC). The clinical activity of nivolumab observed to date suggests the potential for improved outcome as monotherapy.

Nivolumab appears to have a manageable safety profile, which is consistent across completed and ongoing trials. The most common adverse events associated with nivolumab include development of adverse events, the most common of which are inflammatory in nature,

consistent with nivolumab's mechanism of action. Most adverse events were low-grade (Grade 1 to Grade 2) with few high-grade adverse events. Most high-grade adverse events were manageable with the use of corticosteroid and hormone-replacement therapy. Nevertheless, these safety data were established in a population mainly of Caucasians. Therefore, it is possible that Chinese subjects may experience unanticipated adverse events. This protocol has been designed to minimize overall risk to participating subjects. Adverse events will be reviewed expeditiously by the medical monitor and discussed with the study investigators. Also, there are detailed management guidelines for adverse events listed in the protocol.

The potential direct benefit to subjects who participate in this study is that therapy with nivolumab may result in stable disease, partial response or complete response, thus suggesting an acceptable risk to benefit ratio.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., 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 (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

2.3 Informed Consent

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

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

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2 open-label study of nivolumab monotherapy in Chinese subjects with previously treated advanced or recurrent solid tumor. Nivolumab is a fully human monoclonal IgG4 antibody, targeting the programmed death-1 (PD-1) membrane receptor on T-lymphocytes and other cells of the immune system.

The study will consist of 3 periods: screening period (up to 28 days); treatment period (until disease progression or intolerable toxicities); follow-up period (up to 100 days). In dose evaluation phase, each treatment cycle is comprised of 4 doses of assigned study drug (see Table 3.1-1) administered at Days 1, 15, 29 and 43 with a response assessment between Days 49 to 56. The response assessment must be completed before the first dose in the next cycle. In cohort expansion phase, the 3 mg/kg and 240 mg Q2W cohorts will be administered 4 doses in each 8-week treatment cycle, the same as the dose evaluation treatment cycle. The response assessment must be completed before the first dose in the next cycle. The 360 mg Q3W cohort will be administered one dose of study drug in each 3-week treatment cycle. Tumor assessment must be completed every 6 weeks. The 480 mg Q4W cohort will be administered one doses of study drug in each 4-week treatment cycle. Tumor assessment must be completed every 8 weeks.

For subjects enrolled in dose evaluation phase, nivolumab is to be administered over 60 minutes. For subjects enrolled in cohort expansion phase, nivolumab is to be administered over 30 minutes.

Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit.

Table 3.1-1: Nivolumab Dose Levels

Nivolumab Dose Level in Dose Evaluation Phase	Dose
1	3 mg/kg
-1[a]	1 mg/kg
Nivolumab Dose Level in Cohort Expansion Phase	**Dose**
3 mg/kg Q2W	3 mg/kg
240 mg Q2W	240 mg
360 mg Q3W	360 mg
480 mg Q4W	480 mg

[a] Dose level -1 will only be considered if the safety and tolerability profile for 3 mg/kg is evaluated as not acceptable.

In 3 mg/kg cohort and 240 mg Q2W cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 3/Day 1 and will remain in the clinical facility until 24 hours after study drug administration. In 360mg Q3W Cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 6/Day 1 and will remain in the clinical facility until 24 hours after study drug administration. In 480mg Q4W Cohort, for the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 5/Day 1 and will remain in the clinical facility until 24 hours after study drug administration.

Collection of tumor tissue [archival or recent acquisition, formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides] for determination of PD-L1 expression status is highly encouraged. Recent biopsy tissue is preferred when available. Submission of archival tissue is also encouraged for all subjects, irrespective of whether recent biopsy tissue is available. This is not applicable to cohort D.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times (see Time and Events Schedule Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4) throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study.

Approximately 350 mL of blood will be drawn from each subject during the study.

The expected maximum duration of a subject's participation in the study (on-treatment and follow-up periods) is approximately 2.5 years.

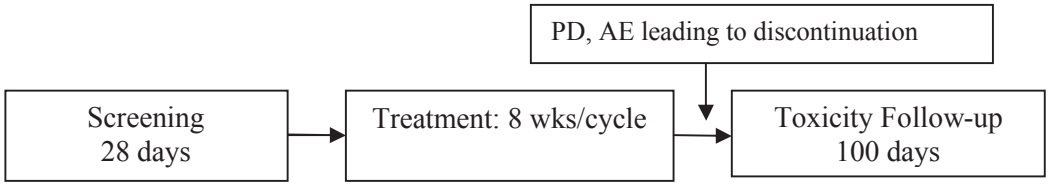
- maximum 28 days of screening,
- maximum of 2 years of therapy,
- approximately 100 days follow-up office visits.

The end of the trial will occur on the day of the last visit of the last subject.

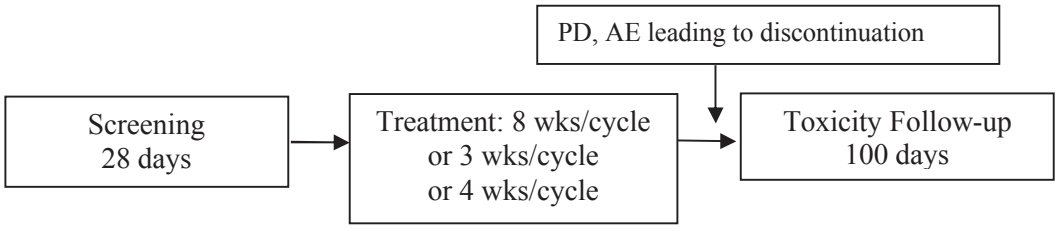
The study design schematic is presented in Figure 3.1-1

Figure 3.1-1: Study Design Schematic

Dose Evaluation Phase



Cohort Expansion Phase



PD= progressive disease; AE= adverse event;

3.1.1 Dose Evaluation Phase

Based on clinical experience with over 300 subjects on up to 2 years of treatment (CA209003/MDX1106-03), the recommended dose of nivolumab during the dose evaluation phase of the study is 3 mg/kg. Dose limiting toxicity (DLT) observation period for each subject is defined as the 1st cycle of treatment (56 days following the first dose). Initially 6 eligible NSCLC subjects will be treated at the dose level of 3 mg/kg. An additional 3 NSCLC subjects may be added to the same dose level, and hence a total number of 6 or 9 subjects will be treated during the dose evaluation phase for a given dose level. A decision to enter cohort expansion phase，or to consider the next lower dose level (1 mg/kg) in dose evaluation phase will be guided by the number of subjects with DLTs observed during the dose evaluation phase (see Table 3.1.1-1). Subjects who do not complete the DLT observation period for reasons other than DLTs will be replaced. A dose level of 1 mg/kg may be considered if the safety and tolerability profile for 3 mg/kg is evaluated as not acceptable, after consultation and agreement between the Investigator(s) and the sponsor as well as review of the existing clinical safety database from earlier studies. Following a similar procedure, if the dose level of 1 mg/kg is evaluated as not acceptable as well, the findings will be discussed between the study investigators and the sponsor and an agreement will be reached as to whether a lower dose of nivolumab should be examined.

Safety monitoring during the dose evaluation phase will be based on the probability of the toxicity given the observed DLTs, with target toxicity of 0.25 (± 0.05).[32] Guidance for safety monitoring after the toxicity outcomes observed is presented in Table 3.1.1-1, and the performance of the design is reported in Appendix 2.

Table 3.1.1-1: Guidance for Safety Monitoring Based on Observed Toxicity Outcomes during the Dose Evaluation Phase

		Number of Subjects Treated	
		6	**9**
Number of Subjects with DLTs	**0**	E	E
	1	S	E
	2	S	E
	3	D	E
	4	NA	D

E: Expand to 56-64 subjects; **S**: Stay at the same dose level by treating additional 3 subjects; **D**: Discuss of proceeding with the next lower dose level.

3.1.2 Cohort Expansion Phase

If the safety and tolerability profile is established at the dose level of 3 mg/kg in the dose evaluation phase, then cohort expansion phase will be initiated, including:

- Cohort A: Continue to accrue up to at least 12 - 20 subjects with solid tumors including but not limited to NSCLC at the dose level of 3 mg/kg;
- Cohort B: Accrue 20 subjects with solid tumors (including but not limited to hepatocellular carcinoma, small cell lung cancer) at the dose level of 240 mg (flat dose) Q2W;
- Cohort C: Accrue up to 12 subjects with solid tumor (including but not limited to gastric cancer, NSCLC) at 360 mg (flat dose) Q3W;
- Cohort D: Accrue up to 12 subjects with solid tumors at 480 mg (flat dose) Q4W.

Clinical safety monitoring of subjects during the cohort expansion phase will be performed. If in a given dose level, the combined incidence exceeds 33% for study drug related toxicity requiring treatment discontinuation, then further enrollment to that dose level will be interrupted and a decision whether or not to continue dosing will be based on discussions of the observed aggregate (acute and chronic) toxicities between the Investigator(s) and the sponsor, if needed. An agreement will be reached as to whether a lower dose should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects to that arm. Depending on preliminary efficacy data, certain tumor types may be expanded to collect additional efficacy data.

3.1.3 Administration of Additional Cycles

Tumor response will be evaluated using RECIST v1.1. In 3 mg/kg cohort and 240mg Q2W cohort, end of cycle tumor response assessment for all subjects will occur between Days 49 to 56 (results of the assessments must be reviewed and documented before the first dose of next cycle). In 360 mg Q3W cohort, tumor assessment must be completed every 6 weeks. In 480 mg Q4W cohort, tumor assessment must be completed every 8 weeks.

Subjects will continue to receive nivolumab treatment until disease progression (or until discontinuation of study therapy in subjects receiving nivolumab beyond progression), discontinuation due to toxicity, withdrawal of consent. The maximum duration of study therapy to be administered to an individual subject in this study is 2 years.

3.1.4 Follow-up Period

- Follow-up begins when decision to discontinue a subject from study therapy is made (no further treatment with nivolumab);
- The first two follow-up visits (follow up #1 and follow up #2) include PK and immunogenicity samples. Follow up #1 = 30 days from last dose ±5 days; Follow up #2 = 70 days from follow up #1 ± 5 days;
- Subjects will be followed for study drug-related toxicities until resolve, return to baseline, or are deemed irreversible.

3.2 Post Study Access to Therapy

At the end of the treatment phase of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

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 (including overnight stays), treatment schedule, laboratory tests and other requirements of the study.

c) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been treated). If re-enrolled, the subject must be re-consented. Obtain agreement from the Medical Monitor prior to re-enrolling a subject.

2. Target Population

a) Chinese subjects with advanced or recurrent solid tumors:

i). histologically or cytologically confirmed

ii). must have failed at least one prior systemic therapy, OR well documented refusal of subjects to receive chemo or biological therapy.

iii). must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (Appendix 3)

b) Life expectancy ≥ 3 months.

c) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 4).

d) Prior systemic cancer therapy must have been completed at least 4 weeks before the study drug administration, and all adverse events have been returned to baseline or stabilized.

e) Prior radiotherapy must have been completed at least 2 weeks before the study drug administration.

f) Immunosuppressive doses of systemic medications, such as steroids (dose >10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration.

g) Prior major surgery requiring general anesthesia must be completed at least 2 weeks before study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects must be recovered. Cutaneous biopsies with only local anesthesia should be completed at least 1 hour prior to study drug administration.

h) Screening laboratory values must meet the following criteria:

i) WBC ⩾ 2000/uL
ii) Neutrophils ⩾ 1500/uL
iii) Platelets ⩾ 100 x 10^3/uL
iv) Hemoglobin ⩾ 9.0 g/dL
v) Creatinine ≤ 1.5 mg/dL or Creatinine Clearance > 40mL/min
vi) AST ≤ 3.0x ULN (AST ≤ 5.0x ULN in HCC patients)
vii) ALT ≤ 3.0x ULN (ALT ≤ 5.0x ULN in HCC patients)
viii) Bilirubin ≤ 1.5 x ULN (except subjects with HCC or Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

i) Hepatocellular carcinoma (HCC) Subjects with the following specific inclusion criteria in addition:

i) Cirrhotic status of Child-Pugh Class A (Appendix 5)

ii) Subjects are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:

- HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or Chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Subjects with chronic HBV infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy.
- HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody

3. Age and Reproductive Status

a) Males and females ≥ 18 years of age.

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

c) Women must not be breastfeeding.

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

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with Nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

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

At a minimum, subjects must agree to the use of one highly effective method listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject and male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
- Progestogen-only hormonal contraception associated with inhibition of ovulation including oral and injectable
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue

to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.2 Exclusion Criteria

Subjects who fulfill any of the following criteria will not be eligible for admission to the study:

1. Target Disease Exceptions

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

b) Subjects with carcinomatous meningitis.

2. Medical History and Concurrent Diseases

a) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

b) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, , or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

d) Active Tuberculosis (TB) infection based on chest X-ray, sputum tests, and clinical examination. Subjects with a history of active TB infection within last 1 year are excluded, even if it was treated. Subjects with a history of active TB infection greater than 1 year ago are excluded unless there is documentation of adequate prior anti-TB treatment.

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

f) Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or topical corticosteroids.

g) Use of other investigational drugs within 28 days or 5 half-lives (whichever is longer) before administration of study drug.

h) Participants who have received a live / attenuated vaccine within 30 days of first treatment.

i) Pregnant or nursing.

j) Inability to be venipunctured and/or tolerate venous access.

k) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

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

m) Any use of systemic or topical corticosteroids at doses > 10 mg/day of prednisone or equivalent within 2 weeks of study drug administration.

n) Any use of traditional medicinal herbal preparations within 2 weeks of study drug administration.

o) HCC subjects with the following specific exclusion criteria in addition

i) Any history of hepatic encephalopathy

ii) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control

iii) Active coinfection with both hepatitis B and C

iv) Hepatitis D infection in subjects with hepatitis B

v) Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or Prothrombin time (PT) ≤ 6 seconds above control

3. Physical and Laboratory Test Findings

a) Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination of adverse events.

b) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

c) Subjects with ≥ Grade 2 peripheral neuropathy.

4. Allergies and Adverse Drug Reaction

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

b) History of any significant drug allergy (such as anaphylaxis) or hepatotoxicity.

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

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

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented 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

All medication administered during the 2 weeks preceding first study drug administration must be recorded in the case report form (CRF) including the name, start and if applicable stop date. Concomitant medication administered during the study must be recorded in the CRF including the generic name and start and end date of therapy. Any change in documented, concomitant medication must also be recorded.

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

1) Any concurrent anti-cancer therapy (chemotherapy, immunotherapy, biologics, extensive radiotherapy, hormone therapy, target therapy, surgery), investigational or approved;
2) Immunosuppressive agents, unless they are utilized to treat an adverse event, and with the exception of those listed in Section 3.4.2.
3) Immunosuppressive doses of systemic corticosteroids (except as stated in the Section 3.4.2.1).
4) Administration of concomitant medication (prescription, over-the-counter or traditional herbal medicine) is prohibited, unless it is prescribed by the investigator for treatment of specific clinical events.

5) Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.

Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to signing informed consent form.

Palliative and supportive care for disease related symptoms may be offered to all subjects on study after dose evaluation period. Palliative (limit-field) radiation therapy is permitted for subjects who have investigator assessed clinical benefit following consultation with BMS medical monitor. Subjects should not receive study treatment during radiation and must meet eligibility criteria prior to resume treatment.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Permitted Corticosteroid Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (i.e., prednisone ≤ 10 mg/day) are permitted. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) or for management of study drug-induced adverse events are permitted.

3.4.3 Antiviral therapy (HCC specific)

Subjects on antiviral therapy for hepatitis B or C should continue the treatment during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the investigator. If a subject has a > 1 log IU/mL increase in HBV DNA, then virologic breakthrough should be considered and HBV DNA confirmed. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a subject has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and treatment with nivolumab temporarily held. The subject may resume treatment with nivolumab once virologic control is reestablished (HBV DNA < 100 IU/mL).

For any subject who continues to be HCV RNA positive after receiving nivolumab, current guidelines for management of chronic HCV infection, including those from AASLD, EASL, or APASL may be consulted. Initiation of direct acting antivirals (DAAs) for HCV is allowed at the discretion of the investigator after discussion with the BMS medical monitor.

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 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 (e.g., infectious disease) illness;
- Inability to comply with protocol;
- Disease progression or clinical deterioration (except treatment beyond progression; see Section 4.3.2.5);
- Dose delay greater than the maximum allowed dosing delay (see Section 4.3.2.3);
- Discretion of the investigator;
- Any adverse event meeting discontinuation criteria (see Section 4.3.2.4).

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

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the CRF page.

3.6 Post Study Treatment Follow up

Subjects who discontinue study treatment may continue to be followed.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study 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;
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g., 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

BMS-936558 100 mg (10 mg/mL) will be packaged in an open-label fashion. Five (5) BMS-936558 10 mL vials will be packaged within a carton. The vials are not subject or treatment group specific although there will be specific vial assignments by subject distributed by the IVRS in order to track drug usage and re-supply.

Product description and storage information is described in Table 4.1-1.

Table 4.1-1: Product Description- Treatment Period

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	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	Store at 2 to 8°C. Protect from light and freezing

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.

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 infusion-related reactions (Section 4.3.2.6).

4.1.3 Storage and Dispensing

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

Investigational product documentation 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 (e.g., 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.

Refer to the BMS-936558 IB and/or pharmacy instruction sheets for details related to handling and dose preparation.

The sites are responsible for procuring their own diluent, IV bags, filters, administration sets, etc.

4.2 Method of Assigning Subject Identification

CA209077 is an open-label study. After it has been determined that the subject meets all eligibility criteria of the study, the subject will be enrolled and a subject number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual. The

investigator (or designee) will register the subject 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

Subjects will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment.

4.2.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered immuno-oncology agents in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: gastrointestinal, renal, pulmonary, pancreatitis, hepatic, endocrinopathies, skin and neurological. The management algorithms can be found in the Nivolumab investigator brochure and Appendix 1 of this protocol.

4.2.1.1 Protocol-specific Recommendations for Management of Hepatic Events in HCC Subjects

The nivolumab program has developed a standardized approach for the management of hepatic events based on cumulative data across the program in subjects with normal hepatic function. Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3x ULN; therefore, only subjects with normal to grade 1 LFTs have been enrolled.

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For HCC subjects to be potentially enrolled in this study, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range are eligible for inclusion. In contrast, the majority of subjects included in prior nivolumab studies have had no higher than a CTCAE grade 1 AST or ALT elevation. Therefore, this requires a protocol-specific approach for the management of hepatic events in HCC subjects, outlined as follows:

- Dose delay criteria for hepatic events are outlined in Appendix 1. If AST or ALT levels do not improve with a dose delay of 3-5 days or if the levels worsen, initiate steroid therapy at 0.5-2 mg/kg/day methylprednisolone or oral equivalent;
- For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1-2 mg/kg/day methylprednisolone or oral equivalent;

- For all subjects initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended;
- If AST or ALT levels do not improve within 3-5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID;
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month

As outlined in Section 4.3.2.3, nivolumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Section 4.3.2.4).

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Dose-limiting Toxicities

Any event listed below, if occurring during Cycle 1 and related to nivolumab, is defined as a DLT.

4.3.1.1 Hepatic DLT

- ALT or AST > 5 and ≤10 ULN for > 2 weeks;
- ALT or AST >10 ULN regardless of duration;
- Total bilirubin > 5 ULN;
- Concurrent ALT or AST > 3 ULN and total bilirubin > 2 ULN.

4.3.1.2 Non-hematologic DLT

- Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1severity within the re-treatment period (14 days) or requires systemic treatment;
- Grade 3 non-skin, drug-related adverse event with the following exceptions:
  - Grade 3 endocrinopathy is not considered as DLT if well controlled with hormone replacement therapy;
  - Grade 3 drug-related laboratory abnormalities without clinical sequelae are not considered as DLTs;
- Grade 4 drug-related AEs, including laboratory abnormalities.

Note that 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 will not be considered DLTs.

4.3.1.3 Hematologic DLT

- Grade 3 drug -related thrombocytopenia associated with bleeding;
- Grade 3 drug-related febrile neutropenia;
- Grade 4 drug-related neutropenia;
- Grade 4 drug-related thrombocytopenia.

4.3.2 Dose Modification

4.3.2.1 Dose Adjustments

There will be no dose adjustment allowed for nivolumab except for weight change (10% or greater increase or decrease) at beginning of each cycle.

4.3.2.2 Dose Delay Criteria

Nivolumab administration should be delayed for the following AEs:

- 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 adverse event;
- Grade 3 drug-related laboratory abnormalities, with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay
  - Grade ≥3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The BMS Medical Monitor should be consulted for such Grade ≥3 amylase or lipase abnormalities.
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a two-fold drug-related increase in AST or ALT or for AST or ALT values 8x ULN (whichever is lower). (HCC patients specific)
- 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 (section 4.3.2.3).

4.3.2.3 Criteria to Resume Dosing

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
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.2.4) should have treatment permanently discontinued
- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met. (HCC patients specific)
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS medical Monitor
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.2.4.

4.3.2.4 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade ≥ 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment;
- Any ≥ Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, diarrhea, colitis, neurologic toxicity, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia lasting > 7 days or associated with bleeding requires discontinuation;
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management algorithm):

- AST or ALT > 5 -10x ULN for > 2 weeks
- AST or ALT > 10x ULN
- Total bilirubin > 5x ULN
- Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Exception: for HCC patients, hepatotoxicity as evidenced by the following:
  - AST or ALT > 10 x ULN for > 2 weeks,
  - AST or ALT > 15 x ULN irrespective of duration,
  - Total bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
  - Concurrent AST or ALT > 3 x ULN and Total bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin.

- Creatinine > 6x ULN
- Any severe or Grade 3 immune-mediated adverse reaction that recurs on reintroduction of Nivolumab, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 immune-mediated adverse reaction that do not recover to Grade 1 or resolve within 12 weeks after the last dose of Nivolumab
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset;
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < grade 4 within 1 week of onset. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities
  - Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any dosing delays lasting > 6 weeks with the following exceptions:
  - Dosing delay to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

  - Dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.3.2.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a subset of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects will be permitted to continue treatment beyond initial RECIST v1.1 defined PD as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression;
2. 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.
3. Tolerance of study drug;
4. Stable performance status;
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).

A follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks) 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 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 (Table 5.1-2, Table 5.1-3, Table 5.1-4). The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records.

For the subjects who continue 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 all target lesions and/ or the development of new measurable lesions. Study therapy should be discontinued if further progression is documented.

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).

4.3.2.6 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, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03) (NCI CTCAE) 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 [e.g., 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 [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of

symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., 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 (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Study drug will be administered in the clinical facility. 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 (e.g., 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, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented;

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4.

Table 5.1-1: Screening Procedural Outline (CA209077) - All Cohorts			
Procedure	**Screening Visit[a]**	**Day -1**	**Notes**
Eligibility Assessments			
Admit to Clinical Facility		x	For the purpose of PK sample collection, subjects will be admitted to the clinical facility the evening prior to dosing (Day -1) for Cycle 1/Day 1 and will remain in the clinical facility until 24 hrs after study drug administration.
Informed Consent	x		A subject is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	x		
Medical History	x		Baseline signs and symptoms are those that are assessed within 2 weeks prior to dosing. Include any toxicities or allergy related to previous treatments.
Concomitant Medication	x	x	All medications taken within 2 weeks of dosing will be recorded.
Diagnosis confirmation and stage	x		
Tumor-specific therapy information	x		
Serology (HCV, HBV & HIV)	x		HBsAg, HCVAb, and HIV Ab. Serology tests must be available and reviewed prior to dosing on Day 1. *For HCC subjects to be potentially enrolled, test following serology for Hep B, Hep C, Hep D: Hep B surface antigen, Hep B surface antibody, Hep B Core antibody, Hep B DNA Viral load (PCR), Hep C viral load (PCR) and Hep C Antibody, Hep D antibody.
Child-Pugh Score (For HCC subjects only)	x		See Appendix 5.
Coagulation profile (For HCC subjects only)	x		Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead.
Safety Assessments			
Complete Physical Examination (PE)	x		
Physical Measurements	x		Includes height and weight.
Vital Signs and Oxygen Saturation	x		Includes body temperature, seated or supine blood pressure and heart rate, respiratory

Table 5.1-1: Screening Procedural Outline (CA209077) - All Cohorts			
Procedure	**Screening Visit[a]**	**Day -1**	**Notes**
			rate, O2 saturation by pulse oximetry at rest. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECOG Performance	x		See Appendix 4.
Laboratory Tests	x		CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN) BUN, creatinine, Ca+, Mg+, Na+, K+, HCO3- (CO2), Cl-, glucose, albumin, T. Protein, TSH, (free T3, Free T4 if TSH not within normal limits); lipase and amylase; Urinalysis including glucose, ketones, pH, blood, leukocyte esterase (leucocyte) and protein. (Note: Microscopic exam of the sediment if blood, protein or leukocyte esterase are positive)
Pregnancy Test	x	x	All WOCBP must have a negative urine or serum β-HCG pregnancy test minimum sensitivity 25 IU/L or equivalent units of HCG within 24 hours before the first infusion; urine pregnancy test at all other timepoints for WOCBP.
Electrocardiogram (ECGs)	x		ECGs should be recorded after the subject has been supine for at least 5 minutes. Baseline ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days prior to study drug administration need not be repeated.
CT/MRI (brain)	x		Baseline imaging done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days prior to study drug administration need not be repeated. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
CT/MRI (chest, abdomen, pelvis and any clinically indicated sites)	x		Baseline imaging done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days prior to study drug administration need not be repeated. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
Archived Tumor Tissue or Recent Tumor Biopsy (optional)	x		May be archival or recent sample. 1 FFPE tissue block, or minimum of 10 FFPE unstained slides are recommended. Submit a copy of the original pathology report along with the sample. Submission of less than 10 unstained slides may be acceptable after approval by BMS Medical Monitor). Tumor tissue collection is not applicable to cohort D per protocol amendment 06.
Adverse Event Reporting			

Table 5.1-1: Screening Procedural Outline (CA209077) - All Cohorts			
Procedure	**Screening Visit[a]**	**Day -1**	**Notes**
Monitor for Serious Adverse Events	x	x	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

[a] Within 28 days of dosing on Day 1

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	29[c]	43[c]	56[c]	1[c]	15[c]	29[c]	43[c]	56[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
Admit to Clinical Facility	x					x							For the purpose of PK sample collection, subjects will be admitted to the clinical facility prior to dosing (Day -1) only on Cycle 1/Day 1 and Cycle 3/Day 1 and will remain in the clinical facility until 24 hrs after study drug administration.
Safety Assessments													
Complete Physical Examination (PE)											x		
Targeted PE	x	x	x	x		x	x	x	x			x	
Physical Measurements	x					x							Weight only. For 3 mg/kg cohort only, dose adjustments are required to be made if there has been a > 10% percent weight change (increase or decrease) since the previous cycle.
Vital Signs and Oxygen Saturation	x	x	x	x		x	x	x	x		x	x	Vital signs should be taken as per institutional standard of care at

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	29[c]	43[c]	56[c]	1[c]	15[c]	29[c]	43[c]	56[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
													visits and prior to, during, and after the infusion with nivolumab. See note in screening procedures.
Electrocardiogram (ECGs)						x							See note in screening procedures.
ECOG Performance	x	x	x	x		x	x	x	x		x	x	See Appendix 4.
Laboratory Tests	x	x	x	x		x	x	x	x		x	x	Within 72 hours prior to dosing. Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN) BUN, creatinine, Ca+, Mg+, Na+, K+, HCO3- (CO2), Cl-, amylase, lipase, glucose, albumin, T.Protein, TSH, (free T3, Free T4 if TSH not within normal limits); Urinalysis including glucose, ketones, pH, blood, leukocyte esterase (leucocyte) and protein. (Note: Microscopic exam of the sediment if blood, protein or leukocyte esterase are positive).

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	**1[c]**	**15[c]**	**29[c]**	**43[c]**	**56[c]**	**1[c]**	**15[c]**	**29[c]**	**43[c]**	**56[c]**	**Last Visit + 30 days (+/- 5 days)**	**Previous Follow-up Visit + 70 Days (+/- 5 days)**	
													Lab results must be reviewed prior to dosing.
Child-Pugh Score (for HCC subjects only)	x	x	x	x		x	x	x	x				Prior to dosing. See Appendix 5.
Coagulation profile (For HCC subjects only)	x	x	x	x		x	x	x	x		x		Prior to dosing.
Viral biomarkers (for HCV and HBV infected HCC subjects)	x										x		For HBV infected--HBV DNA every 4 weeks on treatment. For HCV infected--HCV RNA every 4 weeks on treatment through week 20, then every 12 weeks thereafter.
Review of Concomitant Medications	x										x	x	Should occur at every visit throughout the study.
Monitor for Non-Serious Adverse Events	x										x	x	Should occur at every visit throughout the study.

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	29[c]	43[c]	56[c]	1[c]	15[c]	29[c]	43[c]	56[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
Monitor for Serious Adverse Events	x										x	x	See note in screening procedure.
Pregnancy Test	x	x	x	x		x	x	x	x				See note in screening procedure.
CT/MRI (brain)					x					x			Brain scans during treatment and follow up. periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.
CT/MRI (chest, abdomen, pelvis and any clinically indicated sites)					x					x			
Response Assessment					x					x	x	x	Tumor response status will be assessed by the Investigators using RECIST v1.1. See Appendix 3.
Pharmacokinetic (PK) Assessments													

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	29[c]	43[c]	56[c]	1[c]	15[c]	29[c]	43[c]	56[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
Blood PK Sampling	x										x	x	PK sampling timepoints throughout the study. Refer to Table 5.5.1-1 for specific timepoints. See Section 5.5.
Immunogenicity (ADA) Assessments													
Blood ADA Sample	x										x	x	Refer to Table 5.5.1-1 and Table 5.5.1-2 for specific timepoints.

[redacted]

Table 5.1-2: On Treatment Procedural Outline (CA209077)- 3 mg/kg and 240 mg Q2W Cohorts

Procedure	Treatment										Follow-up[a]		Notes
	Cycle 1					Cycles 2+							
	C1:D1	C1:D15	C1:D29	C1:D43	C1:D56[b]	Cn:D1	Cn:D15	Cn:D29	Cn:D43	Cn:D56[b]	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	29[c]	43[c]	56[c]	1[c]	15[c]	29[c]	43[c]	56[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
[redacted]													
Clinical Drug Supplies													
Study Drug Administration	x	x	x	x		x	x	x	x				Supplied by BMS

[a] When a subject discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic samples taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

[b] This visit is not a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 49 and 56 before administering the first dose of study drug in the next cycle.

[c] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit

Abbreviations: D = Day, C=Cycles (eg.,C1:D1= Cycle 1, Day 1); n=Cycle 2+ as appropriate

Table 5.1-3: On Treatment Procedural Outline (CA209077)- 360 mg Q3W Cohort

Procedure	Treatment (Cycle=21 days)			Follow-up[a]		Notes
	Cycle 1	Cycles 2+				
	C1:D1	Cn:D1	Cn:D21	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	**1[c]**	**1[c]**	**21[c]**	**Last Visit + 30 days (+/- 5 days)**	**Previous Follow-up Visit + 70 Days (+/- 5 days)**	
Admit to Clinical Facility	x					For the purpose of PK sample collection, subjects will be admitted to the clinical facility the evening prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 6/Day 1 and will remain in the clinical facility until 24 hrs after study drug administration.
Safety Assessments						
Complete Physical Examination (PE)				x		
Targeted PE	x	x			x	On Day 1 of each cycle.
Physical Measurements	x	x				Weight only.
Vital Signs and Oxygen Saturation	x	x		x	x	Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab. See note in screening procedures
Electrocardiogram (ECGs)		x				Every other cycle starting Cycle 3. See note in screening procedures.
ECOG Performance	x	x		x	x	See Appendix 4.

Table 5.1-3: On Treatment Procedural Outline (CA209077)- 360 mg Q3W Cohort

Procedure	Treatment (Cycle=21 days)			Follow-up[a]		Notes
	Cycle 1	Cycles 2+				
	C1:D1	Cn:D1	Cn:D21	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	1[c]	21[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
Laboratory Tests	x	x		x	x	Within 72 hours prior to dosing. Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN) BUN, creatinine, Ca+, Mg+, Na+, K+, HCO3- (CO_2), Cl-, amylase, lipase, glucose, albumin, T.Protein, TSH, (free T3, Free T4 if TSH not within normal limits); Urinalysis including glucose, ketones, pH, blood, leukocyte esterase (leucocyte) and protein. (Note: Microscopic exam of the sediment if blood, protein or leukocyte esterase are positive). **Lab results must be reviewed prior to dosing.**
Child-Pugh Score (for HCC subjects only)	x	x				Prior to dosing. See Appendix 5.
Coagulation profile (For HCC subjects only)	x	x		x		Prior to dosing.
Viral biomarkers (for HCV and HBV infected HCC	x			x		For HBV infected--HBV DNA every 3 weeks on treatment. For HCV infected--HCV RNA every 3 weeks on

Table 5.1-3: On Treatment Procedural Outline (CA209077)- 360 mg Q3W Cohort

Procedure	Treatment (Cycle=21 days)			Follow-up[a]		Notes
	Cycle 1	Cycles 2+				
	C1:D1	Cn:D1	Cn:D21	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	1[c]	21[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
subjects)						treatment through week 18, then every 12 weeks thereafter.
Review of Concomitant Medications	x			x	x	Should occur at every visit throughout the study.
Monitor for Non-Serious Adverse Events	x			x	x	Should occur at every visit throughout the study.
Monitor for Serious Adverse Events	x			x	x	See note in screening procedure.
Pregnancy Test	x	x				See note in screening procedure.
CT/MRI (brain)			x[b]			Brain scans during treatment and follow up. periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.
CT/MRI (chest, abdomen, pelvis and any clinically			x[b]			

Table 5.1-3: On Treatment Procedural Outline (CA209077)- 360 mg Q3W Cohort

Procedure	Treatment (Cycle=21 days)			Follow-up[a]		Notes
	Cycle 1	Cycles 2+				
	C1:D1	Cn:D1	Cn:D21	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	**1[c]**	**1[c]**	**21[c]**	**Last Visit + 30 days (+/- 5 days)**	**Previous Follow-up Visit + 70 Days (+/- 5 days)**	
indicated sites)						
Response Assessment			x[b]	x	x	Every 6 weeks. Tumor response status will be assessed by the Investigators using RECIST v1.1. See Appendix 3.
Pharmacokinetic (PK) Assessments						
Blood PK Sampling	x			x	x	PK sampling timepoints throughout the study. Refer to Table 5.5.1-2 for specific timepoints. See Section 5.5.
Immunogenicity (ADA) Assessments						
Blood ADA Sample	x			x	x	Refer to Table 5.5.1-2 for specific timepoints.

[redacted]

Table 5.1-3: On Treatment Procedural Outline (CA209077)- 360 mg Q3W Cohort

Procedure	Treatment (Cycle=21 days)			Follow-up[a]		Notes
	Cycle 1	Cycles 2+				
	C1:D1	Cn:D1	Cn:D21	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	1[c]	21[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
[redacted]						
Clinical Drug Supplies						
Study Drug Administration	x	x				Supplied by BMS

[a] When a subject discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic samples taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

[b] This visit is not a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments will begin at week 6 post first dose date (± 7 days) and be performed every 6 weeks (± 7 days) subsequently.

[c] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit

Abbreviations: D = Day, C=Cycles (eg.,C1:D1= Cycle 1, Day 1); n=Cycle 2+ as appropriate

Table 5.1-4: On Treatment Procedural Outline (CA209077)- 480 mg Q4W Cohort

Procedure	Treatment (Cycle=28 days)					Follow-up[a]		Notes
	Cycle 1		Cycles 2+					
	C1:D1	C1:D15	Cn:D1	Cn:D15	Cn:D28	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	1[c]	15[c]	28[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
Admit to Clinical Facility	x		x					For the purpose of PK sample collection, subjects will be admitted to the clinical facility the evening prior to dosing (Day -1) only for Cycle 1/Day 1 and Cycle 5/Day 1 and will remain in the clinical facility until 24 hrs after study drug administration.
Safety Assessments								
Complete Physical Examination (PE)						x		
Targeted PE	x		x				x	On Day 1 of each cycle.
Physical Measurements	x		x					Weight only.
Vital Signs and Oxygen Saturation	x		x			x	x	Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab. See note in screening procedures
Electrocardiogram (ECGs)			x					Every other cycle starting Cycle 3. See note in screening procedures.

Table 5.1-4: On Treatment Procedural Outline (CA209077)- 480 mg Q4W Cohort

Procedure	Treatment (Cycle=28 days)					Follow-up[a]		Notes
	Cycle 1		Cycles 2+					
	C1:D1	C1:D15	Cn:D1	Cn:D15	Cn:D28	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	1[c]	15[c]	28[c]	Last Visit + 30 days (+/- 5 days)	Previous Follow-up Visit + 70 Days (+/- 5 days)	
ECOG Performance	x		x			x	x	Please see Appendix 4.
Laboratory Tests	x	x	x	x		x	x	On D1 and D15 in Cycles 1 to 5. On D1 only in Cycles 6+. Within 72 hours prior to dosing. Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN) BUN, creatinine, Ca+, Mg+, Na+, K+, HCO3- (CO_2), Cl-, amylase, lipase, glucose, albumin, T.Protein, TSH, (free T3, Free T4 if TSH not within normal limits); Urinalysis including glucose, ketones, pH, blood, leukocyte esterase (leucocyte) and protein. (Note: Microscopic exam of the sediment if blood, protein or leukocyte esterase are positive). **Lab results must be reviewed prior to dosing.**
Review of Concomitant Medications	x					x	x	Should occur at every visit throughout the study.
Monitor for Non-Serious Adverse Events	x					x	x	Should occur at every visit throughout the study.

Table 5.1-4: On Treatment Procedural Outline (CA209077)- 480 mg Q4W Cohort

Procedure	Treatment (Cycle=28 days)					Follow-up[a]		Notes
	Cycle 1		Cycles 2+					
	C1:D1	C1:D15	Cn:D1	Cn:D15	Cn:D28	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	**1[c]**	**15[c]**	**1[c]**	**15[c]**	**28[c]**	**Last Visit + 30 days (+/- 5 days)**	**Previous Follow-up Visit + 70 Days (+/- 5 days)**	
Monitor for Serious Adverse Events	x					x	x	See note in screening procedure.
Pregnancy Test	x		x					See note in screening procedure.
CT/MRI (brain)					x[b]			Brain scans during treatment and follow up. periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.
CT/MRI (chest, abdomen, pelvis and any clinically indicated sites)					x[b]			
Response Assessment					x[b]	x	x	Every 8 weeks. Tumor response status will be assessed by the Investigators using RECIST v1.1. See Appendix 3.
Pharmacokinetic (PK) Assessments								

Table 5.1-4: On Treatment Procedural Outline (CA209077)- 480 mg Q4W Cohort

Procedure	Treatment (Cycle=28 days)					Follow-up[a]		Notes
	Cycle 1		Cycles 2+					
	C1:D1	C1:D15	Cn:D1	Cn:D15	Cn:D28	Follow-up 1	Follow-up 2	
Timepoint Per Cycle (Day)	1[c]	15[c]	1[c]	15[c]	28[c]	**Last Visit + 30 days (+/- 5 days)**	**Previous Follow-up Visit + 70 Days (+/- 5 days)**	
Blood PK Sampling	x					x	x	PK sampling timepoints throughout the study. Refer to Table 5.5.1-3 for specific timepoints. See Section 5.5.
Immunogenicity (ADA) Assessments								
Blood ADA Sample	x					x	x	Refer to Table 5.5.1-3 for specific timepoints.
Clinical Drug Supplies								
Study Drug Administration	x		x					Supplied by BMS

[a] When a subject discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic samples taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

[b] This visit is not a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments will begin at week 8 post first dose date (± 7 days) and be performed every 8 weeks (± 7 days) subsequently.

[c] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit

Abbreviations: D = Day, C=Cycles (eg.,C1:D1= Cycle 1, Day 1); n=Cycle 2+ as appropriate

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.03;
- Nivolumab Investigator Brochure;
- Pharmacy binder;
- Laboratory manuals for collection and handling of blood (including PKs [redacted] and immunogenicity) and tissue specimens;
- Site manual for operation of interactive voice response system;
- Enrollment worksheets;
- Serious Adverse Event (or eSAE) case report form pages;
- Pregnancy Surveillance Forms.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to dosing. The baseline physical examination should include weight, height, BP, HR, and temperature. These should be performed within 28 days of treatment. Concomitant medications will be collected from within 2 weeks prior to treatment assignment through the study treatment period.

Toxicity assessments will be continuous during the treatment phase until 100 days (equal to approximately 5 half lives of nivolumab) after the last dose of nivolumab.

Adverse events and laboratory values will be graded according to the NCI CTCAE version 4.03.

Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab. The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last exam, report these changes on the appropriate AE or SAE page.

Additional measures including non-study required laboratory tests should be performed as clinically indicated.

5.3.1 Imaging Assessment for the Study

CT with contrast of the chest, abdomen, pelvis and any clinically indicated sites are to be performed for tumor assessments at the timepoints outlined in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4.

CT scans should be acquired with ≤5mm slices with no intervening gap (contiguous). Should a subject have a contraindication for CT IV contrast, a non contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of ≤5 mm and <2mm gap (preferably no gap / contiguous). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging timepoints.

MRI brain scans during on-study treatment and follow up periods are required **only** if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest CNS involvement.

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.

5.3.2 Laboratory Test Assessments

Results of clinical laboratory tests performed on Day -1 visit must be available prior to dosing.

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (e.g., provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3 Laboratory Test Result Abnormalities).

Please refer to Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4 for required laboratory tests and schedule.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4. Baseline assessments should be performed within 28 days of study treatment. Chest, abdomen, pelvis and any clinically indicated sites as determined by the investigator should be assessed at baseline. Subsequent assessments should utilize the same imaging modality. Subjects will be evaluated for tumor response every 8 weeks from the first dose of study drug until tumor progression is documented.

Change in tumor measurements and tumor response will be assessed by the investigator using the RECIST v1.1 criteria (Appendix 3).

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

Not applicable.

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing

Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3 list the sampling schedule to be followed for the assessment of nivolumab pharmacokinetics and immunogenicity for all cohorts. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected predose should be taken just prior to the administration, and end-of-

infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). If the infusion was interrupted, the reason for interruption should also be documented on the CRF. Blood samples will be processed to collect serum. The serum samples will be analyzed for nivolumab by validated methods. Further details of blood collection, labeling, processing, storage and shipping will be provided to the site in the procedure manual.

Table 5.5.1-1: Pharmacokinetics and Immunogenicity Sampling Schedule for 3 mg/kg Q2W (Dose Evaluation and Cohort Expansion) and 240 mg Q2W

CYCLE (1 CYCLE = 8 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample	ADA Blood Sample
1	1	Predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15	predose[b]	336:00	X	X
	29	predose[b]	00:00	X	X
2	1	predose[b]	00:00	X	X
3	1	predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15	predose[b]	336:00	X	
5	1	predose[b]	00:00	X	X
7	1	predose[b]	00:00	X	X
Day 1 of every 2 cycles after C7 until discontinuation of Study Treatment	1	predose[b]	00:00	X	X

Table 5.5.1-1: Pharmacokinetics and Immunogenicity Sampling Schedule for 3 mg/kg Q2W (Dose Evaluation and Cohort Expansion) and 240 mg Q2W

CYCLE (1 CYCLE = 8 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample	ADA Blood Sample
First 2 Follow-up Visits (EXCEPT for subjects that WITHDRAW CONSENT)[d]				X	X

[a] If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single pharmacokinetic sample will be taken at that visit.

[b] Predose samples should be collected on the day of dosing just prior to the start of the infusion

[c] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion. In the event of a delay beyond 30 min, the sample should be taken immediately prior to the actual END of the infusion. For subjects in the evaluation phase receiving nivolumab over 60 min infusion, EOI sample will be collected immediately prior to the infusion stopping time at 60 min.

[d] Pharmacokinetic and immunogenicity samples will be taken at Follow-up Visits.

Table 5.5.1-2: Pharmacokinetics and Immunogenicity Sampling Schedule for, 360 mg Q3W

CYCLE (1 CYCLE = 3 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample	ADA Blood Sample
1	1	Predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15		336:00	X	
2	1	predose[b]	00:00	X	X
4	1	predose[b]	00:00	X	X
6	1	predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15		336:00	X	
7	1	predose[b]	00:00	X	
11	1	predose[b]	00:00	X	X
Day 1 of every 6 cycles after C11 until discontinuation of Study Treatment	1	predose[b]	00:00	X	X

Table 5.5.1-2: Pharmacokinetics and Immunogenicity Sampling Schedule for, 360 mg Q3W

CYCLE (1 CYCLE = 3 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample	ADA Blood Sample
First 2 Follow-up Visits (EXCEPT for subjects that WITHDRAW CONSENT)[d]				X	X

[a] If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single pharmacokinetic sample will be taken at that visit.

[b] Predose samples should be collected on the day of dosing just prior to the start of the infusion.

[c] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion. In the event of a delay beyond 30 min, the sample should be taken immediately prior to the actual END of the infusion.

[d] Pharmacokinetic and immunogenicity samples will be taken at Follow-up Visits.

Table 5.5.1-3: Pharmacokinetics and Immunogenicity Sampling Schedule for 480 mg Q4W

CYCLE (1 CYCLE = 4 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample	ADA Blood Sample
1	1	Predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15		336:00	X	X
2	1	predose[b]	00:00	X	X
3	1	predose[b]	00:00	X	X
5	1	predose[b]	00:00	X	X
		EOI[c]	00:30	X	
			04:00	X	
			08:00	X	
	2		24:00	X	
	3		48:00	X	
	5		96:00	X	
	8		168:00	X	
	15		336:00	X	
6	1	predose[b]	00:00	X	X
Day 1 of every 4 cycles after C6 until discontinuation of Study Treatment	1	predose[b]	00:00	X	X
First 2 Follow-up Visits (EXCEPT for subjects that WITHDRAW CONSENT)[d]				X	X

[a] If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single pharmacokinetic sample will be taken at that visit.

[b] Predose samples should be collected on the day of dosing just prior to the start of the infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[c] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). In the event of a delay beyond 30 min, the sample should be taken immediately prior to the actual END of the infusion.

[d] Pharmacokinetic and immunogenicity samples will be taken at Follow-up Visits.

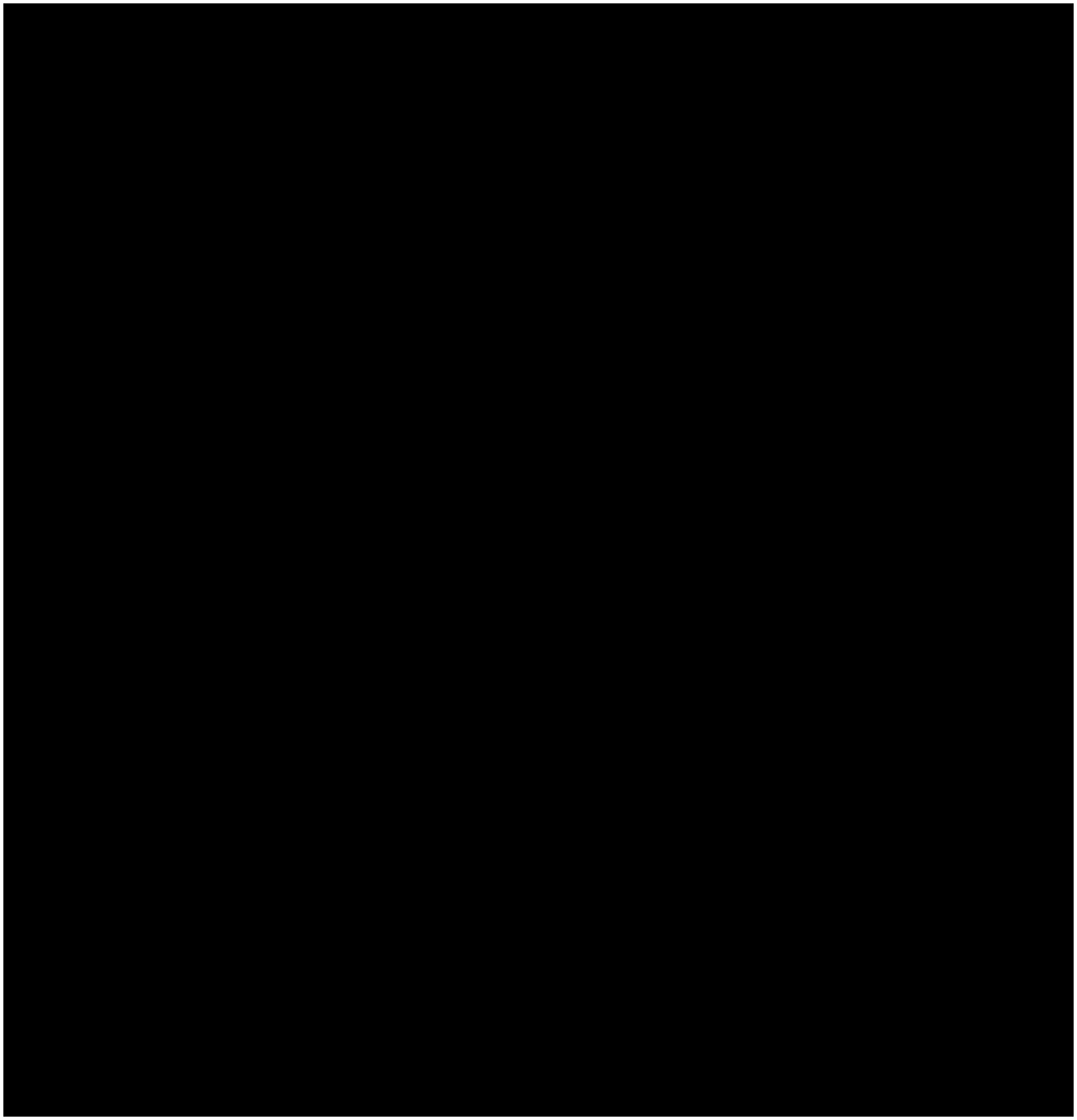
5.5.2 Pharmacokinetics and Immunogenicity Sample Analyses

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3. PK and immunogenicity samples will be analyzed for nivolumab and nivolumab anti-drug antibodies, respectively, by validated immunoassays. [redacted] Serum samples designated for PK assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

[redacted]



[redacted]

[redacted]

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

Not applicable

5.10 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

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

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

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

BMS will be reporting adverse events to regulatory authorities and ethics committees according

to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal

Regulations 21 CFR Parts 312 and 320.

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 [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.).

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.4 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 (e.g., routine colonoscopy).
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period

and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

An SAE report must 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 must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). 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 (e.g., 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 drug exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

The following definition takes into account anticipated baseline compromise of liver function in patients with HCC.

Potential drug induced liver injury is defined as:

- Concurrent ALT ≥ 10 x ULN, AND
- Total bilirubin ≥ 2 times ULN or baseline value (if elevated bilirubin at study entry), AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This is a Phase 1/2 safety trial and the sample size during the dose evaluation phase depends on the observed toxicity. Six or 9 NSCLC subjects per dose level will be treated according to the Guidance for Safety Monitoring as shown in Table 3.1.1-1. Utilizing the information on the observed toxicity of related AEs with Grades 3 and 4 (16%) among 304 subjects in a multidose, dose-ascending study with nivolumab monotherapy in subjects with selected advanced or recurrent malignancies (CA209003/MDX1106-03), there is a less than 20% posterior probability with this guidance that the toxicity rate could be 40% or higher, for different total number of subjects (6 or 9) in the dose evaluation phase, as shown in Table 8.1-1 (all numbers in the third column are less than 20%). The posterior probability calculations assume a Beta(1, 4) prior distribution, which implies a toxicity rate around 20% as estimated from CA209003/MDX1106-03 study. Similarly, there is a less than 10% posterior probability that the toxicity rate could be 45% or higher for the dose evaluation phase (all numbers in the last column of Table 8.1-1 are less than 10%).

Table 8.1-1: Posterior Probability of Toxicity Rate based on an Observed Number of Subjects with DLTs

Number of Subjects Treated	Observed Number of Subjects with DLTs*	P(toxicity rate ≥ 40%|Data)	P(toxicity rate ≥ 45%|Data)
6	0	0.006	0.003
	1	0.046	0.023
	2	0.167	0.0996
9	0	0.001	<0.001
	1	0.013	0.005
	2	0.058	0.027
	3	0.169	0.093

* The number of subjects with DLTs allowed by the Guidance for Safety Monitoring Based on Observed Toxicity Outcomes during the Dose Evaluation Phase as described in Table 3.1.1-1.

If the safety and tolerability profile is established at a dose level in the dose evaluation phase, then that dose level will be expanded to a total of 20 PK evaluable subjects. A subject will be considered PK evaluable when an adequate sampling has been completed during Cycle 1. In the event of a higher than expected dropout rate prior to PK sampling in Cycle 3, additional subjects may be enrolled to reach an adequate number of subjects with PK profiles in Cycle 3.

One of the objectives of expansion cohorts is to characterize the pharmacokinetics (PK) of nivolumab in Chinese subjects in different dosing regimens. The sample size of 12-20 in the expansion cohorts is adequate to characterize PK within a dosing group.

Approximately 6-9 subjects are expected to be enrolled in dose evaluation and expanded to approximately 56-64 in total.

8.2 Populations for Analyses

The following subject populations will be used in the study:

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS;
- All treated subjects: All subjects who received at least one dose of study medication;
- Pharmacokinetic Population: All subjects who received any nivolumab and have available concentration time data;
- Immunogenicity Population: All subjects who received nivolumab and have at least pre-and 1 post treatment immunogenicity measurement;
- [redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective is to characterize the safety, tolerability of nivolumab in Chinese subjects. The primary objective will be measured by:

- Number and percent of subjects that experience drug-related grade 3-4 AEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];
- Number and percent of subjects that experience drug-related grade 3-4 SAEs occurring up to 100 days after the last dose of study drug. [Time Frame - On a continuous basis up to 100 days after the last dose of study drug];

Number and percent of subjects with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.03 (as assessed at the planned times listed in Table 5.1-1, Table 5.1-2, Table 5.1-3, and Table 5.1-4). [Time Frame - On a continuous basis up to 100 days after the last dose of study drug].

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

The secondary objective of characterizing the PK of nivolumab in Chinese subjects will be measured by nivolumab PK parameters derived from serum concentration versus time data, as described in Section 5.5. The pharmacokinetic parameters to be assessed, if data permits, in all cohorts include but are not limited to:

Cmax - Maximum observed serum concentration

Tmax - Time of maximum observed serum concentration

In addition, the following parameters will be determined for all subjects:

AUC(0-T) -Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration.

AUC(TAU) - Area under the concentration-time curve in one dosing interval

Ceoinf - Serum concentration achieved at the end of study drug infusion

Ctrough - Trough observed serum concentration at the end of dosing interval

Ctau - Concentration at the end of dosing interval

AI - Accumulation index; calculated based on ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau)

T-HALFeff - Effective elimination half-life that explains the degree of observed AUC accumulation.
CLT - Total body clearance

8.3.2.2 Immunogenicity

The secondary objective relating to immunogenicity will be measured by the ADA status both at the sample level and at the subject level. At the sample level a sample is characterized as baseline ADA-positive, ADA-positive or ADA-negative to each study drug. At the subject level, relevant ADA endpoints include proportion of subjects with a Baseline ADA-positive sample, and proportion of ADA-positive subjects for each study drug. Time points for collection are specified in Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3. Additional details will be presented in the SAP.

8.3.2.3 Anti-tumor response

The secondary objective of assessing the anti-tumor response of nivolumab will be measured by the following endpoints at subject level:

- Best overall response (BOR) by investigator using Response Evaluation Criteria in Solid Tumor (RECIST v1.1);
- Duration of response: is computed for subjects with a BOR of CR or PR, and defined as the time between the date of first response and the subsequent date of objectively documented disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment;

The following efficacy endpoints for each tumor type may be summarized by dose and/or across dose depending on data availability.

- Objective response rate (ORR) is defined as the proportion of all treated subjects whose best overall response (BOR) is either a complete response (CR) or partial response (PR) by investigator using Response Evaluation Criteria in Solid Tumor (RECIST v1.1);
- Median duration of response
- Response rate at 24 weeks: is defined as the proportion of all treated subjects who has CR or PR by 24 weeks.

- Disease control rate (DCR) at 24 weeks is defined as the proportion of all treated subjects who has CR, PR or SD by 24 weeks

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and disease baseline pertinent characteristics will be summarized by dose level and tumor type and overall using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum for continuous variables; n and percent for categorical variables).

8.4.2 Efficacy Analyses

Individual subject's BOR will be listed by dose and/or across dose if appropriate for each tumor type based on RECIST v1.1. BOR outcomes will be tabulated, by dose and/or across dose if appropriate, for each tumor type depending on data availability.
Individual subject's DOR will be listed by dose and/or across dose if appropriate for each tumor type.
The following analysis for each tumor type may be summarized by dose and/or across dose depending on data availability.
ORR will be calculated and corresponding two-sided 95% exact confidence intervals using Clopper and Pearson method will be provided by dose and/or across dose for each tumor type depending on data availability.
Response rate and disease control rate at 24 weeks will be estimated by Kaplan-Meier analysis of time to response and the corresponding two-sided 95% confidence interval by Greenwood formula will be provided by dose and /or across dose for each tumor type depending on data availability.
Median duration of response will be estimated by Kaplan-Meier analysis and corresponding two-sided 95% confidence intervals by Greenwood formula will be provided by dose and/or across dose for each tumor type as appropriate.

8.4.3 Safety Analyses

All recorded AEs will be coded according to the most current version of MedDRA and listed by dose level and tumor type and overall. AEs will be summarized for each dose level and tumor type and overall by system organ class and preferred term using the worst grade within each category within a subject. Toxicity changes from baseline in clinical laboratory test results will be summarized by dose level and tumor type and overall using the worst on-treatment CTC grade values. Vital signs, ECGs and clinical laboratory test results will be listed and summarized by dose level and tumor type and overall.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for PK parameters of nivolumab as specified in Section 5.5. by dosing schedule and study cycle as appropriate. Ctrough will be summarized for all subjects. To assess attainment of steady state, plots of Ctrough versus time will be provided for all subjects. Pharmacokinetic concentrations of nivolumab from all subjects will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Immunogenicity analyses

Data from the assessment of immunogenicity markers will be listed by subjects. Number and frequency of ADA response classifications will be summarized by dosing regimen. The details of the ADA response classifications will be provided in the study statistical analyses plan (SAP) document.

8.5 Interim Analyses

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

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. Certain CRF pages and/or electronic files may serve as the source documents:

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

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

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or

entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers);
- Involvement in trial design;
- Other criteria (as determined by the study team).

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
APC	adenomatous polyposis coli
aPTT	activated partial thromboplastin time
ASR	age standardized rate
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius

Term	Definition
Cavg	average concentration
Cexpected-tau	expected concentration in a dosing interval
CD28	Cluster of differentiation 28
CFR	Code of Federal Regulations
CI	confidence interval
CLcr	creatinine clearance
CLT	total body clearance
Cmax, CMAX	maximum observed concentration
CNS	central nervous system
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTC	common toxicity criteria
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
DC	discontinue
dL	deciliter
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	Electronic Case Report Form
eg	exempli gratia (for example)
EGFR-TKI	epidermal growth factor receptor tyrosine kinase inhibitors
ECOG	Eastern Cooperation Oncology Group
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
eSAE	electronic (submission) of SAE
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

Term	Definition
g	gram
GCP	Good Clinical Practice
G criteria	adjusted R^2 value of terminal elimination phase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mAbs	monoclonal antibodies
mg	milligram
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mPFS	median PFS

Term	Definition
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NCCM	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	nanogram
NIMP	non-investigational medicinal products
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
SAE	serious adverse event
SD	standard deviation
SLD	sum of the longest diameters
SmPC	summary of product characteristics
SOP	Standard Operating Procedures
sp.	species
T	time
[redacted]	[redacted]
TCR	T-Cell Receptor
T-HALFeff	Effective elimination half life that explains the degree of AUC accumulation observed
Tmax, TMAX	time of maximum observed concentration

Term	Definition
ULN	upper limit of normal
WOCBP	women of childbearing potential

12 REFERENCES

1 Pardoll D. Does immune system see tumors as foreign or self? Annu Rev Immunol 2003; 21: 807-30.

2 Zhao P, Dai M, Chen WQ, Li N. Cancer trends in China. JPN J Clin Oncol 2010; 40(4): 281-285.

3 Wang YC, Wei LJ, Liu JT, Li SX, Wang QS. Comparison of cancer incidence between China and the USA. Cancer Biol Med. 2012 June; 9(2): 128-132.

4 Globocan (Globocan 2008 data)

5 Tsunehiro T, Yoshiro S, Yuko K. Gastric Cancer: current status of diagnosis and treatment. Cancers 2013, 5, 48-63.

6 China Cancer Registry Report (2009)

7 Lee A, et al. The battle against nasopharyngeal cancer. Radiotherapy and Oncology 2012, 104: 272-278.

8 Qing X, Xie M, Jiang G. Present situation and development of chemotherapy in nasopharyngeal cancinoma. J Clin Otorhinolaryngol Head Neck Surg(China) 2013; 27 (3).

9 Ma BB,Hui EP,Chan AT. Systemic approach to improving treatment outcome in nasopharyngeal carcinoma: Current and future directions. Cancer Sci 2008; 99(7) : 1311-1318.

10 Foo KF, et al. Systemic approach to improving treatment outcome in nasopharyngeal carcinoma: Current and future directions. Annals of Oncology 2002; 13: 150-156.

11 Chua D, et al. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. JPN J Clin Oncol 2008; 38(4): 244-249.

12 Drew M. Pardoll. The blockade of immune checkpoints in cancer immunotherapy. Nature Review. 2012; Apr:252-264.

13 Nishimura H, Honjo T. PD-1: an inhbitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001; 22: 265-8.

14 Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000; 192: 1027-34.

15 Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001; 2: 261-8.

16 Carter LL, Fouser LA, Jussif J, et al. PD-1:PD-l1 inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. Eur J Immunol. 2002; 32: 634-43.

17 Sharpe AH, Wherry EJ, Ahmed R, Freeman GI. The function of programmed death 1 and its ligands in regulating autoimmunity and infections. Nat Immunol. 2007; 8(3): 239-45.

[18] Thompson RH, Gillett MD, Cheville JC, et al. Costumulatory B7-H1 in renal cell carcinoma patients: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci. 2004; 101(49): 17174-9.

[19] Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res. 2004; 10 (15): 5094-100.

[20] Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003; 63: 6501-5.

[21] Azuma T, Yao S, Zhu G, Flies A, Flies S, Chen L. BY-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood 2008; 111 (7): 3535-3643.

[22] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005; 104 (10): 2084-2091.

[23] Wu C, Zhu Y, Jiang J, et al. Immunohistochemical localization of programmed death-1 ligand (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem. 2006; 108 (1): 19-24.

[24] Nomi T, Sho S, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 pathway in human pancreatic cancer. Clin. Cancer Res. 2007; 13 (7): 2151-2157.

[25] Clinical Study Report: MDX1106-03 (CA209003). A Phase 1, Open-Label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX1106) in Subjects with Selected Advanced or Recurrent Malignancies. Bristol-Myers Squibb Company; 2013. Document Control No. 930044417.

[26] Nivolumab Investigator Brochure version 14 (30-Jun-2015)

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

[28] Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (ChckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015 Mar; 16(3): 257-65.

[29] Julie Brahmer, Karen L. Reckamp, Paul Bass, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med, 2015 May 31. [Epub ahead of print]

[30] Luis Paz-Ares, Leora Horn, Hossein Borghaei, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). 2015 ASCO, LBA 109.

[31] Non-Clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1); BMS DCN 930067627 1.0

[32] Ji et al. 2009, Clinical Trials 2010; 7: 653–663.

APPENDIX 1 MANAGEMENT OF SAFETY ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

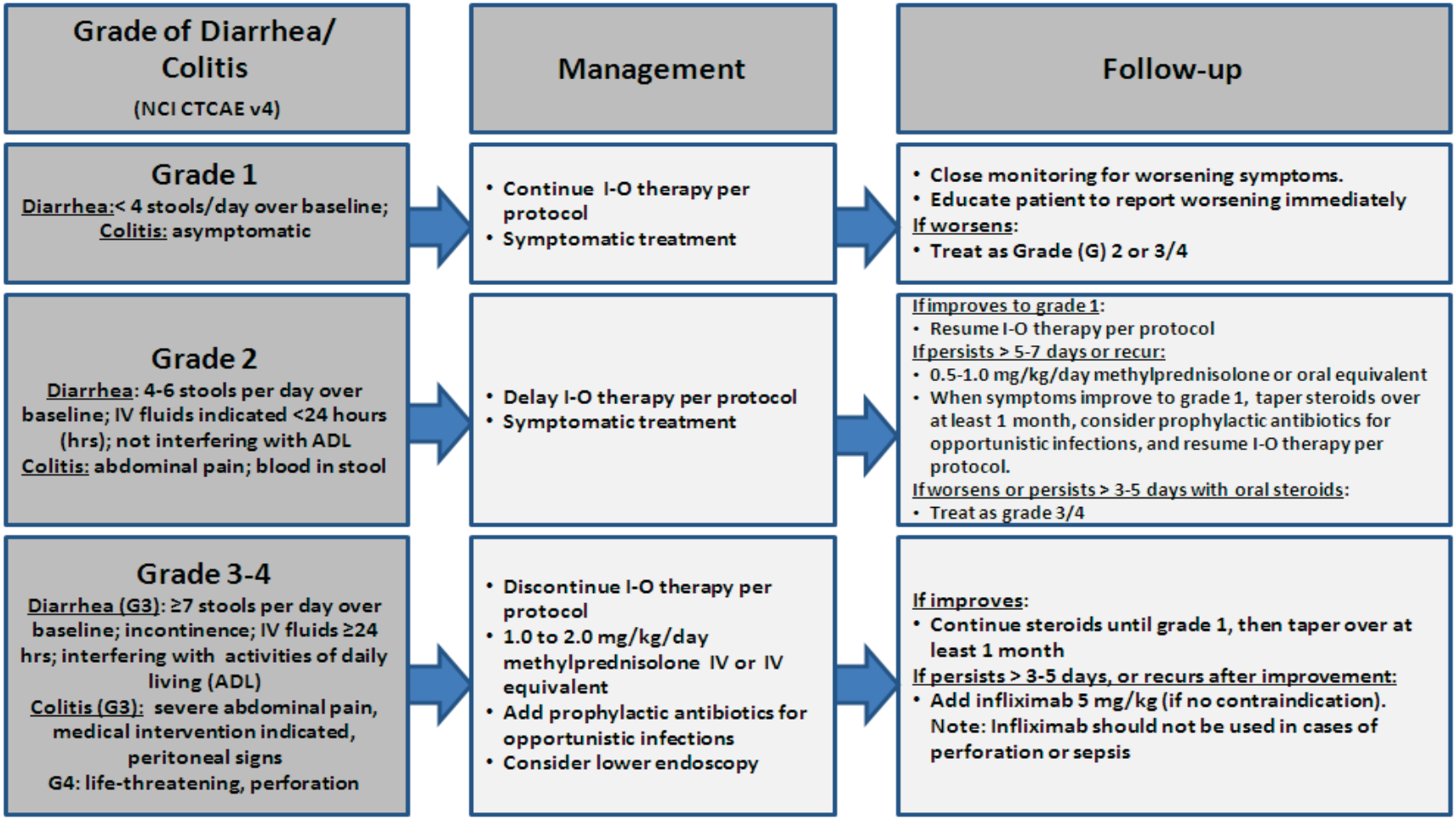
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

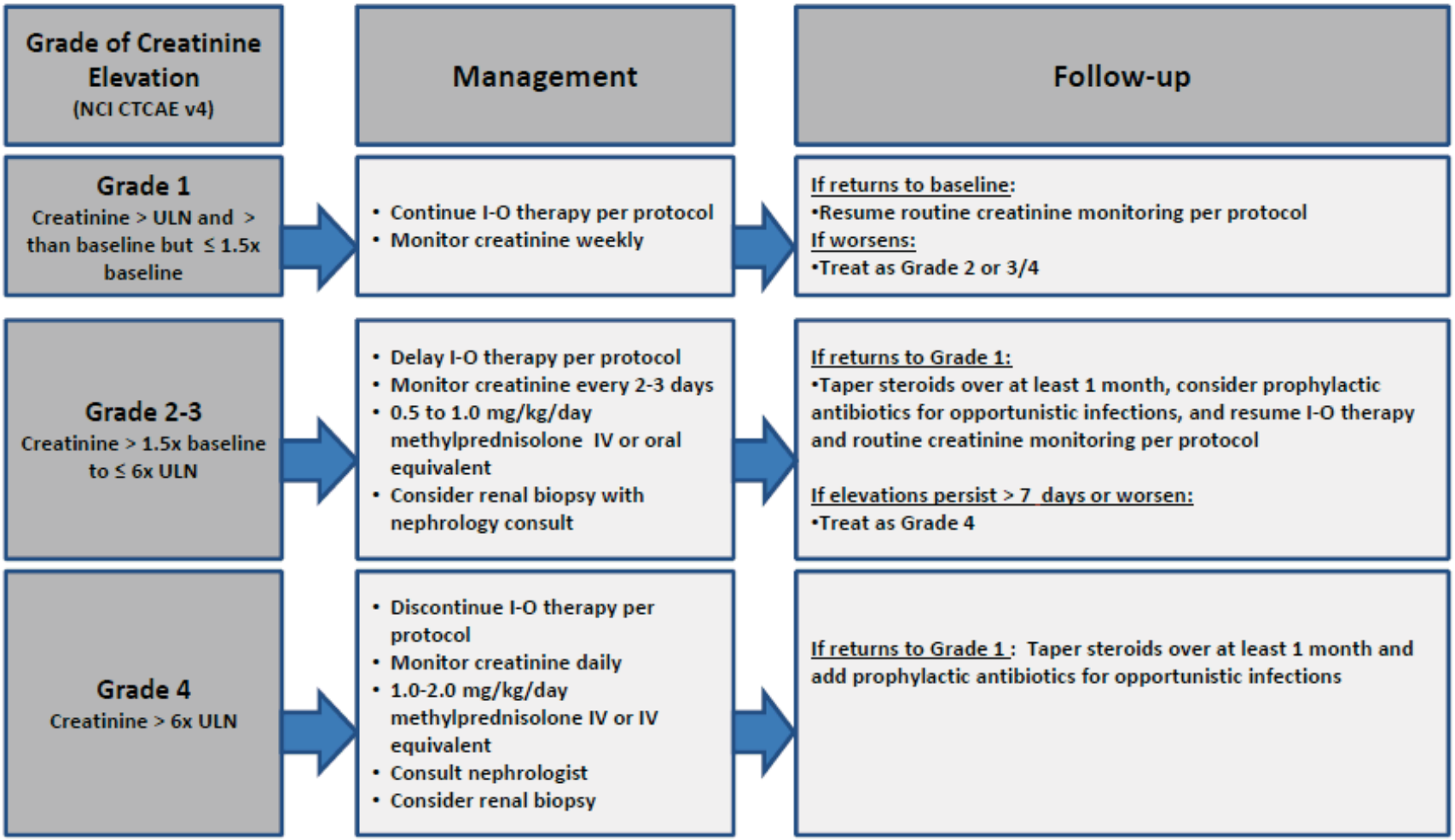
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

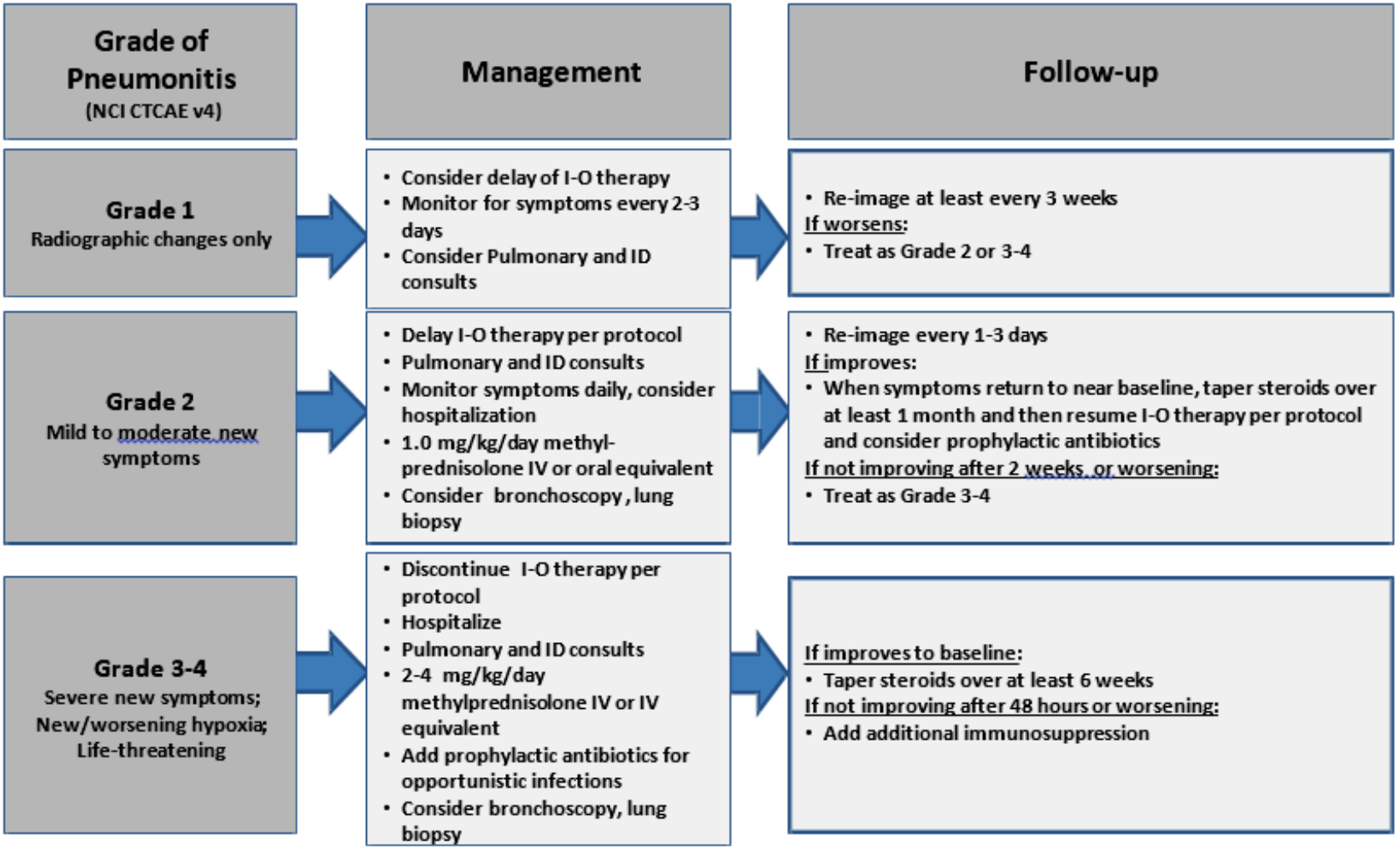
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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

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.

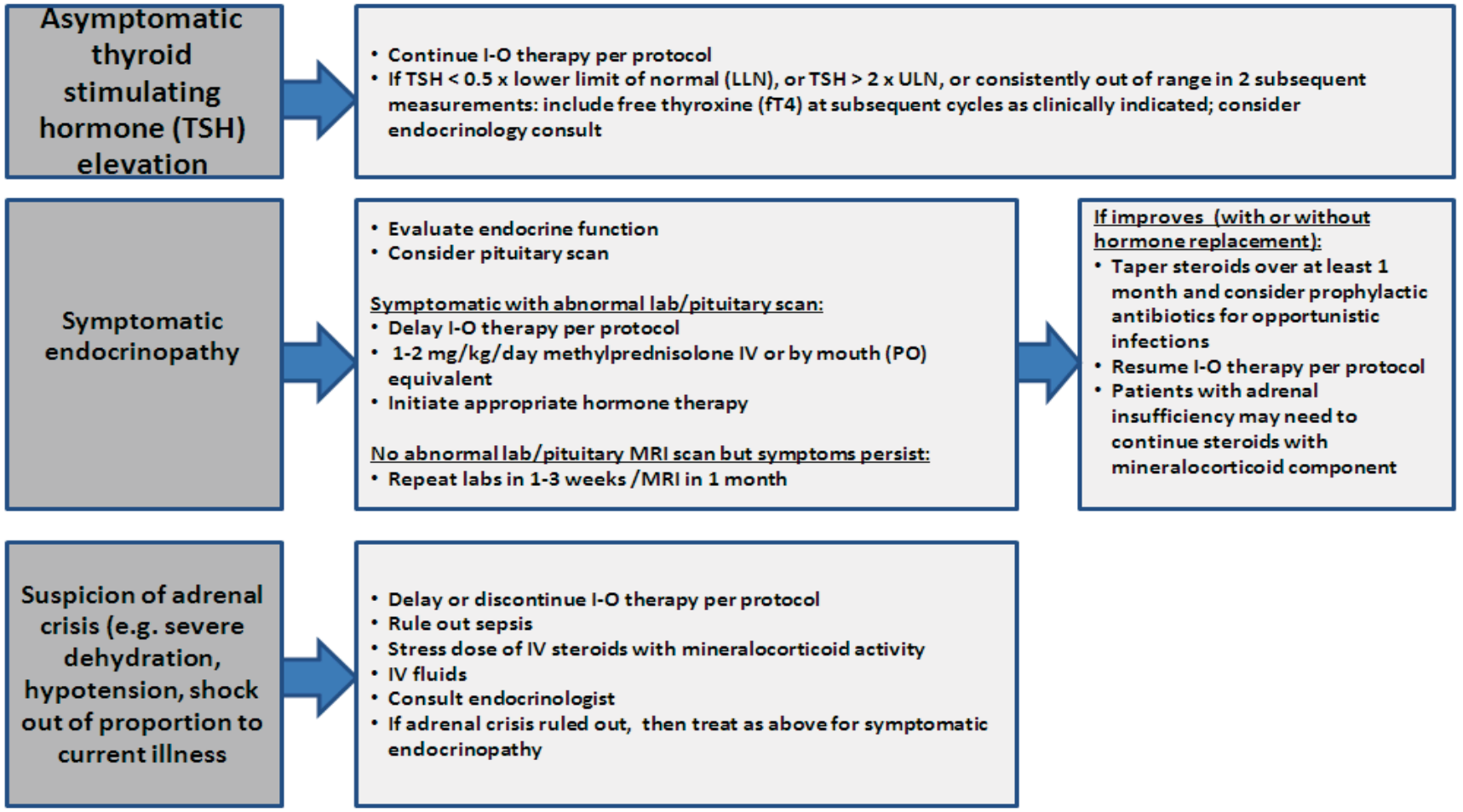
Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 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.

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

Endocrinopathy Management Algorithm

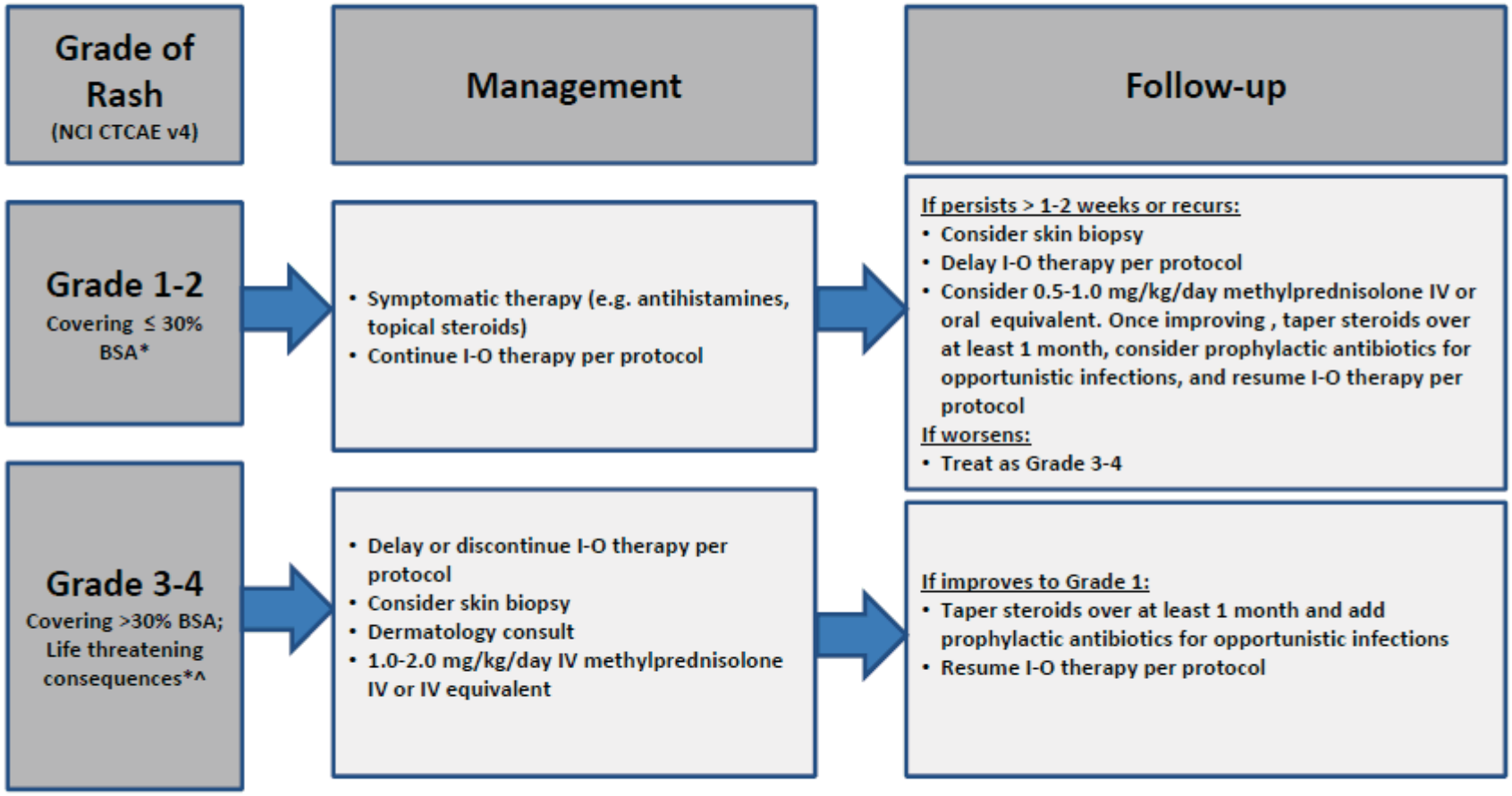
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

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.

Neurological Adverse Event Management Algorithm

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

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

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

APPENDIX 2 SIMULATION TO EXAMINE PROBABILITY-BASED DESIGN VS. ALGORITHM BASED A+B DESIGNS

Guidance for safety monitoring during the dose evaluation phase listed in Table 1 is based on the probability of toxicity given observed DLTs, with a target toxicity of 0.25 (± 0.05). The target toxicity of 0.25 (± 0.05) gives 3 intervals in the toxicity probability scale: (0, 20%) that is considered lower than the target toxicity rate, [20%, 30%] that is considered within the toxicity target range, and (30%, 100%) that is considered toxic. For simplicity, we refer to this design as the probability-based design.

Using this probability-based design, during the dose evaluation phase, initially 6 eligible subjects will be treated at the dose level of 3 mg/kg. An additional 3 subjects may be added to the same dose level, i.e. a total number of 6 or 9 subjects will be treated during the dose evaluation phase for a given dose level. A decision to stay at the same dose level (3 mg/kg) by treating an additional 3 subjects, to expand to 20 subjects, or to consider the next lower dose level (1 mg/kg), will be guided by the number of subjects with dose-limiting toxicities (DLTs) observed during the dose evaluation phase (see Table 1). Subjects who do not complete the DLT observation period for reasons other than DLTs will be replaced, where the DLT observation period for each subject is defined as the 1st cycle of treatment (56 days of dosing). A dose level of 1 mg/kg may be considered if the safety and tolerability profile for 3 mg/kg is evaluated as not acceptable, after consultation and agreement between the Investigator(s) and the sponsor as well as review of the existing clinical safety database from earlier studies. Following a similar procedure, if the dose level of 1 mg/kg is evaluated as not acceptable as well, the findings will be discussed between the study investigators and the sponsor and an agreement will be reached as to whether a lower dose of nivolumab should be examined.

Table 1: Guidance for Safety Monitoring Based on Observed Toxicity Outcomes during the Dose Evaluation Phase

		Number of Subjects Treated	
		6	**9**
Number of Subjects with DLTs	**0**	E	E
	1	S	E
	2	S	E
	3	D	E
	4	NA	D

E: Expand to 20 subjects;

S: Stay at the same dose level by treating additional 3 subjects;

D: Discuss of proceeding with the next lower dose level

Simulations were conducted to examine the performances of the probability-based design and the algorithm-based A+B designs (including a 3+3 design and a 6+3 design) for this study. The 3+3 design starts from the higher dose level (3 mg/kg); adapts every cohort of 3 patients; considers the next dose level if unacceptable toxicity rate observed. The 6+3 design is a variation of the 3+3 design, which starts with 6 subjects instead of 3 subjects and then adapts a cohort of 3 subjects afterwards. The "1/3" Rule has been used in these two designs, in the way that:

- If the observed toxicity rate is <1/3 in the first cohort of subjects (3 subjects for the 3+3 design and 6 subjects for the 6+3 design), then this dose level will be considered safe to continue to the dose expansion phase;
- If the observed toxicity rate is 1/3 in the first cohort of subjects, then another 3 subjects will be enrolled to evaluate this dose level further;
- If the observed toxicity rate is >1/3 in the first cohort of subjects, then this dose level will be considered too toxic and proceeding with the next lower dose level will be discussed;
- If the observed toxicity rate is <1/3 in the two cohorts of subjects together (6 subjects in total for the 3+3 design and 9 subjects in total for the 6+3 design), then this dose level will be considered safe to continue to the dose expansion phase;
- If the observed toxicity rate is ≥1/3 in the two cohorts of subjects together, then this dose level will be considered as too toxic and proceeding with the next lower dose level will be discussed.

The probability-based design is knowledge-driven, which assumes a target toxicity rate. On the contrary, the algorithm-based A+B design is algorithm-driven, which uses the "1/3" rule.

Simulation implementation:

- 1000 simulated trials
- Probability-based design as described above
- Algorithm-based 6+3 design as described above
- Algorithm-based 3+3 design as described above

Toxicity scenarios for each dose level:

Dose	1mg	3mg
C1:	0.20,	0.30
C2:	0.15,	0.30
C3:	0.20,	0.25
C4:	0.15,	0.25
C5:	0.15,	0.20
C6:	0.10,	0.20
C7:	0.10,	0.15

Assumption: Monotonicity

Simulation results:

Table -2: Simulation Results Summary

		% Selected		Avg. tox rate (%)
		1 mg/kg	3 mg/kg	
Scenario 1	**Tox level**	**0.20**	**0.30**	
Probability-based	% MTD	32.8	67.2	27.4
Algorithm-based 3+3	% MTD	50.0	50.0	28.9
Algorithm-based 6+3	% MTD	47.8	52.2	29.6
Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (67.2% vs 50.0% or 52.2%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (50.0% or 47.8% vs 32.8%); the average toxicity rates for the probability-based design is lower than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].				
		% Selected		**Avg. tox rate (%)**
		1 mg/kg	**3 mg/kg**	
Scenario 2	**Tox level**	**0.15**	**0.30**	
Probability-based	% MTD	36.2	63.8	26.7
Algorithm-based 3+3	% MTD	50.0	50.0	28.9
Algorithm-based 6+3	% MTD	47.8	52.2	29.6
Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (63.8% vs 50.0% or 52.2%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (50.0% or 47.8% vs 36.2%); the average toxicity rates for the probability-based design is lower than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].				
		% Selected		**Avg. tox rate (%)**
		1 mg/kg	**3 mg/kg**	
Scenario 3	**Tox level**	**0.20**	**0.25**	
Probability-based	% MTD	22.4	77.6	24.2
Algorithm-based 3+3	% MTD	40.0	60.0	22.8
Algorithm-based 6+3	% MTD	34.1	65.9	23.6
Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (77.6% vs 60.0% or 65.9%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (40.0% or 34.1% vs 22.4%); the average toxicity rates for the probability-based design is higher than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].				

Table -2: Simulation Results Summary

		% Selected		Avg. tox rate (%)
		1 mg/kg	3 mg/kg	
Scenario 4	**Tox level**	**0.15**	**0.25**	
Probability-based	% MTD	22.8	77.2	22.9
Algorithm-based 3+3	% MTD	40.0	60.0	22.8
Algorithm-based 6+3	% MTD	34.1	65.9	23.6

Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (77.2% vs 60.0% or 65.9%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (40.0% or 34.1% vs 22.8%); the average toxicity rates for probability-based design is between that of the algorithm-based A+B designs and within the interval of [0.2, 0.3].

		% Selected		Avg. tox rate (%)
		1 mg/kg	3 mg/kg	
Scenario 5	**Tox level**	**0.15**	**0.20**	
Probability-based	% MTD	13.9	86.1	19.5
Algorithm-based 3+3	% MTD	30.2	69.8	17.7
Algorithm-based 6+3	% MTD	22.0	78.0	18.7

Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (86.1% vs 69.8% or 78.0%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (30.2% or 22.0% vs 13.9%); the average toxicity rates for probability-based design is higher than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].

		% Selected		Avg. tox rate (%)
		1 mg/kg	3 mg/kg	
Scenario 6	**Tox level**	**0.10**	**0.20**	
Probability-based	% MTD	13.7	86.3	19.1
Algorithm-based 3+3	% MTD	30.2	69.8	17.7
Algorithm-based 6+3	% MTD	22.0	78.0	18.7

Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (86.3% vs 69.8% or 78.0%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (30.2% or 22.0% vs 13.7%); the average toxicity rates for probability-based design is higher than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].

Table -2: Simulation Results Summary

		% Selected		Avg. tox rate (%)
		1 mg/kg	3 mg/kg	
Scenario 7	**Tox level**	**0.10**	**0.15**	
Probability-based	% MTD	7.1	92.9	15.3
Algorithm-based 3+3	% MTD	18.6	81.4	11.9
Algorithm-based 6+3	% MTD	11.2	88.8	13.8

Note: Probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs (92.9% vs 81.4% or 88.8%); the algorithm-based A+B designs select sub-optimal dose level (1 mg/kg) more frequently (18.6% or 11.2% vs 7.1%); the average toxicity rates for probability-based design is higher than the algorithm-based A+B designs, closer to the target toxicity rate of 25% and within the interval of [0.2, 0.3].

In summary, the probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs for all the scenarios evaluated. The average toxicity rates for probability-based design are closer to the target toxicity rate of 25% in most cases, except for scenario 4, where three average toxicity rates are close to each other. The algorithm-based A+B designs are more conservative than the probability-based design, and tend to select sub-optimal dose (1 mg/kg) more frequently.

In summary, the probability-based design selects the correct dose (3 mg/kg) more frequently than the algorithm-based A+B designs for all the scenarios evaluated. The average toxicity rates for probability-based design are closer to the target toxicity rate of 25% in most cases, except for scenario 4, where three average toxicity rates are close to each other. The algorithm-based A+B designs are more conservative than the probability-based design, and tend to select sub-optimal dose (1 mg/kg) more frequently.

APPENDIX 3 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.2 Non-Measurable

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

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

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

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

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

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

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

3.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

3.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they

need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

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

3.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

3.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

3.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

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

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 3.3.2B is to be used.

Table 3.3.2A: Time Point Response: Patients With Target (± Non-Target) Disease

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

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

Table 3.3.2B: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease and NE = inevaluable

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point

of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3.

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

Table 3.3.3: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration [b]met, otherwise, NE
NE	NE	NE

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

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

[b] Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than

28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649 - 655, 1982

APPENDIX 5 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate