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CLINICAL PROTOCOL CA186107

A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced /Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma

Revised Protocol Number: 06
Incorporates amendment 01 through 06, 08, and Administrative Letter 01 through 05

[redacted]

Medical Monitor

Roland Meier, M.D., Ph.D.

[redacted]

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Research and Development
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium
Route 206 & Province Line Road
Lawrenceville, NJ 08543

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	22-Mar-2017	Incorporates Amendment 08
Amendment 08	22-Mar-2017	In order to further explore an emerging efficacy signal, additional patients with previously untreated metastatic melanoma (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) subjects with PD-L1 negative tumors (<1%) will be enrolled under this amendment.
Revised Protocol 05	09-May-2016	Incorporates Amendment 06 and Administrative Letters 04 and 05
Amendment 06	09-May-2016	To include a cohort of NSCLC and melanoma subjects who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1 therapy.
Administrative Letter 05	01-Jun-2016	To clarify application to new cohort of subjects with NSCLC and melanoma who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1) therapy and exception for NSCLC and MEL subjects enrolling in the expansion cohorts where prior anti-PD-1 or anti-PD-L1 therapies are specifically required.
Administrative Letter 04	19-Jan-2016	Change in MM
Revised Protocol 04	22-Dec-2015	Incorporates Amendment 05
Amendment 05	22-Dec-2015	To expand the study population for cohort expansion to include subjects with follicular lymphoma and to further differentiate subjects with non-small-cell lung cancer into two separate groups (those with no prior anti PD-1/anti-PD-L1 therapy and those who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1.
Revised Protocol 03	30-Aug-2015	Incorporates Amendment 04 and Administrative Letter 03
Amendment 04	30-Aug-2015	Discontinue enrollment into Cohorts A, B, C, D. Implement an update to exclusion Criteria
Admin Letter 03	26-Aug-2015	Discontinue enrollment into Cohorts A, B, C, D during cohort expansion
Revised Protocol 02	29-Jun-2015	Incorporates Amendment 03
Amendment 03	29-Jun-2015	To implement a change in duration to combination therapy and use of flat dosing for subjects enrolled following approval of Revised Protocol 02
Revised Protocol 01	06-Mar-2015	Incorporate Amendment 02
Amendment 02	06-Mar-2015	To implement changes to inclusion/exclusion criteria, clarify requirements and assessments for treatment beyond disease progression and criteria for allowing treatment to resume after a dose delay due to toxicity, add time and events schedules for subjects eligible for retreatment, and clarify PK sampling and biomarker assessments.

Document	Date of Issue	Summary of Change
Adm Letter 02	21-Oct-2014	To correct a typographical error and to clarify that drug preparation, storage, handling and dispensing of nivolumab is contained in the Investigator Brochure and/or pharmacy reference sheets, and the interval between end of nivolumab dose and beginning of urelumab dose.
Adm Letter 01	30-Sep-2014	To correct PK sample time points and clarify the expected time points for vital signs and observation period of subjects post-dosing.
Original Protocol	10-Jun-2014	Not applicable

SYNOPSIS

Clinical Protocol CA186107

Protocol Title: A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced /Metastatic Solid Tumors and B Cell Non-Hodgkin's Lymphoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered intravenous (IV) doses of urelumab (BMS-663513) every 4 and nivolumab (BMS-936558) every 2 weeks, for up to 48 weeks of study therapy.

Retreatment with the combination at the dose and regimen assigned at study entry, within 12 months of last treatment with study drug, may be permitted after discussion and agreement with the BMS Medical Monitor.

Study Phase: 1/2

Research Hypothesis:

It is anticipated that the combination of an anti-CD137 (urelumab) and an anti PD-1 antibody (nivolumab) will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical testing. There is no formal primary research hypothesis for this study to be statistically tested.

Objectives:

Primary Objective: To assess the safety and tolerability of urelumab given in combination with nivolumab and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination, in subjects with advanced (metastatic and/or unresectable) solid tumors and B cell lymphomas.

Secondary Objectives:

- To assess the preliminary anti-tumor activity of the combination of urelumab and nivolumab in subjects with advanced solid tumors and B cell lymphomas.
- To characterize the pharmacokinetics (PK) of urelumab and nivolumab when co-administered.
- To monitor immunogenicity of urelumab and nivolumab administered as combination therapy.

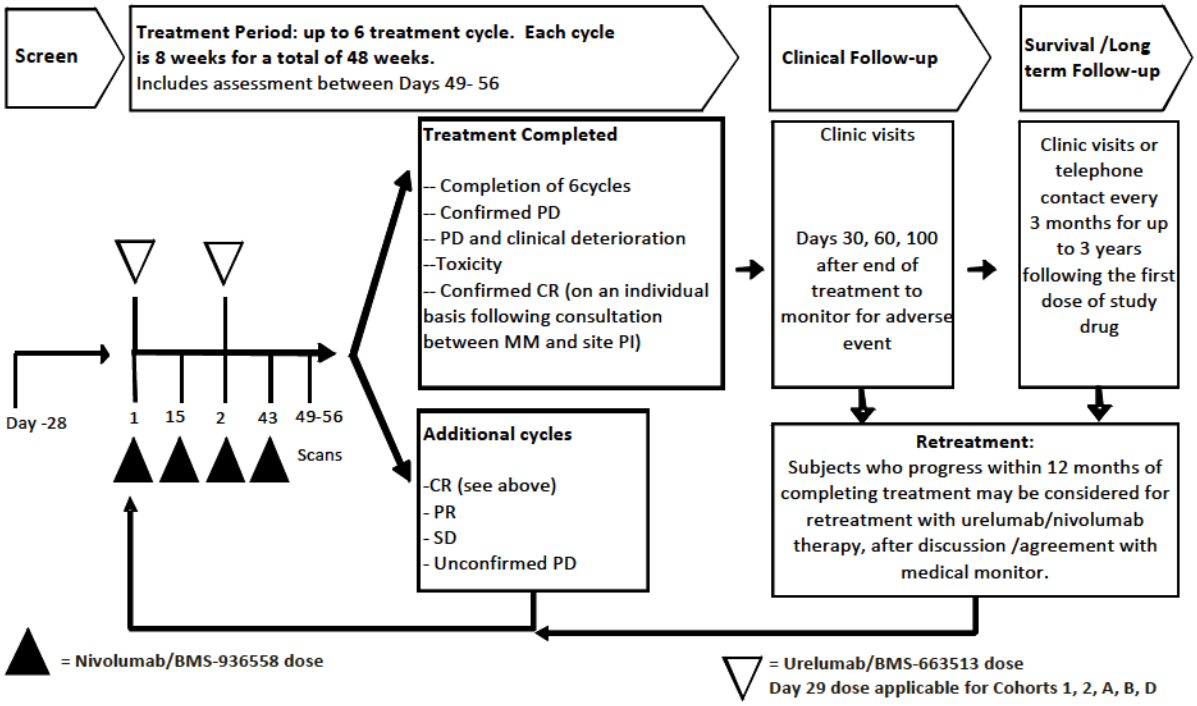
[redacted]

Study Design:

This is a phase 1/2 open label study. The first phase of the study will consist of a dose escalation assessment of the safety and tolerability of urelumab administered with nivolumab in subjects with advanced solid tumors or B-cell non-Hodgkin's lymphoma (NHL). The second phase of the study will include a 2-stage cohort expansion in multiple tumor types (melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, and follicular lymphoma) at the maximally tolerated dose (MTD), highest administered dose (HAD), or at an alternative dose/regimen as determined by the investigators and the sponsor and outlined in the Study Population section (Section 3.3).

The study design schema is outlined below in Figure 1:

Figure 1: Study Design Schema



CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Subjects will complete up to four periods of the study:

Screening (up to 28 days):

Subjects will sign consent and be evaluated for study eligibility.

Treatment (up to a maximum of 6 cycles of study therapy):

The Treatment Period will consist of up to 6 treatment cycles. Each cycle is 8 weeks for a total of 48 weeks. Nivolumab will be given every 2 weeks up to 48 weeks. Urelumab will be given every 4 weeks up to 48 weeks. On days where both study drugs are given, nivolumab will be given first followed by urelumab.

Clinical/Safety Follow-up (100 days following study drug discontinuation):

Subjects that discontinue the treatment phase will enter the Clinical/Safety Follow-up period, with visits scheduled on days 30, 60 and 100 to monitor for adverse events.

Survival/Long-Term Follow-up (survival will last up to 3 years following the first dose of study drug):

The duration of survival follow-up will be up to 3 years following the first dose of study drug. Subjects who discontinue study drug with ongoing SD, PR, or CR will continue to have tumor assessments completed every

12 weeks for the first year after discontinuation of study drug, and then continue to receive scans as per standard of care guidelines for follow-up or at a minimum of every 6 months for up to 3 years following the first dose of study drug, or until disease progression or withdrawal of consent. Subjects in the Survival/Long-term Follow-up period who have progression of disease will be allowed to receive tumor directed therapy as required.

Re-treatment with the combination at the dose and regimen assigned at study entry, within 12 months of last dose of study drug, may be permitted after discussion and agreement with the BMS Medical Monitor, provided that the subject continues to meet the re-treatment eligibility criteria. These subjects will complete up to 4 additional periods of the study: screening, treatment, clinical follow-up, and survival/long-term follow-up.

Dose Escalation:

A 3+3+3 design will be used to assess the safety of urelumab given in combination with nivolumab. The cohorts for dose escalation are provided in Table 1. Potential alternate cohorts are provided in Table 3. The Dose Limiting Toxicity (DLT) observation period will last for 8 weeks following the first dose of study medication. The DLT evaluation period is defined as 8 weeks after administration of the first combination dose of nivolumab and urelumab, and includes subjects who have had administration of at least one dose of nivolumab monotherapy during this interval. This interval is based upon inclusion of the earliest times to onset of clinically significant adverse events attributed to study drug, and also allows for a substantial amount of time for unexpected toxicities related to dosing regimen to emerge.

Approximately three subjects will be treated initially at each dose regimen. In order to assure sufficient evaluable subjects per cohort an additional subject may be added to a cohort (ie, enroll a fourth subject in a cohort of 3).

Note: Should this action be taken, cohort tolerability assessment and subsequent dose escalation, if indicated, will occur when the minimum number of subjects required to assess tolerability have completed the 8 week DLT period. However, if any additional subject experiences an event that would, per protocol, result in either cohort expansion or the halting of dose escalation, the escalation rules as defined below in Table 2 will be followed.

Table 1: Doses/Regimens During Dose Escalation

Cohort Number	Total Subjects[a]	urelumab	nivolumab[b]
1	n = approximately 3-9	3 mg IV every 4 weeks	3 mg/kg or 240 mg IV every 2 weeks
2	n = approximately 3-9	8 mg IV every 4 weeks	3 mg/kg or 240 mg IV every 2 weeks
Total	n = approximately 6-18		

[a] 3-9 subjects will be enrolled during dose escalation. Additional subjects may be added for a total of up to 12 subjects per dose level

[b] Nivolumab 3 mg/kg will be administered for subjects enrolled prior to Revised Protocol 02. Nivolumab 240 mg flat dose administered for subjects enrolled after Revised Protocol 02

After dose escalation to the next cohort, 3-9 additional subjects may be enrolled in any previously tolerated dose level (original 3-9 subjects from dose escalation plus additional subjects required to have a total cohort size of 12. If the rate of DLTs exceeds 33% in a given treatment regimen; the findings will be discussed and further enrollment may be interrupted for that specific treatment regimen and tumor type. If one of the planned dose cohorts is determined to exceed the MTD, and/or based on ongoing safety/tolerability experience through the dose escalation phase of the study, an alternate dose escalation schema as outlined in Table 3 may be explored in consultation and agreement between the Sponsor and investigators.

Sentinel Subject: During dose escalation, the first subject in each cohort will receive C1D1 (eg, the first dose of study drugs) and be observed for 3 weeks such that one combination dose followed by one nivolumab dose are administered before additional subjects in the cohort receive the first dose of study drug (ie, C1D1).

Dose Escalation Rules:

Table 2 outlines the decision rules for dose escalation based on the number of subjects and observed DLTs. No intra-subject dose escalation or reduction is allowed. Subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same dose level/regimen. Dose escalation will be based on the number of dose limiting toxicities (DLTs) experienced during the DLT observation period

If dose escalation is terminated, then the dose or dose regimen below that which invoked the stopping rule will be declared the MTD.

Table 2: Decision Rules During Dose Escalation

Number of Evaluable Subjects/ Cohort	**3-4**			**6-8**			**9-12**	
Total Number of Observed DLTs	0	1	2 or more	1	2	3 or more	2	3 or more
Decision Rule	Dose Escalate	Enroll additional subjects at in cohort to reach at least 6 subjects	Dose exceeds MTD	Dose Escalate	Enroll additional subjects at in cohort to reach at least 9 subjects	Dose exceeds MTD	Dose Escalate	Dose exceeds MTD

If either Cohort 1 or Cohort 2 exceeds the MTD, alternate treatment regimens may be explored during dose escalation or cohort expansion (listed in Table 3).

Table 3: Alternate Treatment Regimens

Cohort	**urelumab**	**nivolumab**[a]
A[b]	8 mg IV every 8 weeks	3 mg/kg or 240 mg IV every 2 weeks
B[b]	8 mg IV every 8 weeks	1 mg/kg or 80 mg IV every 2 weeks
C	3 mg IV every 4 weeks	1 mg/kg or 80 mg IV every 2 weeks
D[b]	3 mg IV every 8 weeks	3 mg/kg or 240 mg IV every 2 weeks

[a] Nivolumab 1 mg/kg or 3 mg/kg will be administered for subjects enrolled prior to Revised Protocol 02. Nivolumab 80 mg or 240 mg flat dose administered for subjects enrolled after Revised Protocol 02

[b] Treatment regimen not applicable following Revised Protocol 03.

All available clinical and laboratory data observed during dose escalation will be reviewed to determine the alternative treatment regimen listed in Table 3 to be evaluated. The nature, time of onset, and time to resolution of DLTs observed will be reviewed in the context of the current safety data from the respective urelumab and

nivolumab trials. After review of this data, and after consultation between the investigators and the sponsor, the identified alternative treatment regimens may be evaluated.

Cohort Expansion:

The purpose of the cohort expansions is to gather additional safety, tolerability, preliminary efficacy and pharmacodynamic information regarding the combination of urelumab and nivolumab. Once the MTD of combined administration of urelumab and nivolumab has been defined, cohort expansions will be initiated.

Expansion cohorts will follow a 2-stage design as defined below in Table 4:

Table 4: Cohort Expansion

Tumor Types	Stage 1 Expansion	Stage 2 Expansion
Non-small Cell Lung Cancer (NSCLC)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Melanoma (MEL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Head and Neck Squamous Cell Carcinoma (SCCHN)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Diffuse Large B Cell Lymphoma (DLBCL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
NSCLC (progressive or recurrent disease during or after anti-PD-1/anti-PD-L1 therapy)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Follicular Lymphoma (FL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Melanoma (progressive or recurrent disease during or after an anti-PD-1/anti-PD-L1 containing treatment regiment)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Melanoma PD-L1 negative	Up to approximately 50 subjects at MTD or HAD	

Stage 1 of the expansion phase will treat 20 subjects per tumor type at the MTD and HAD as identified during dose escalation followed by Stage 2: continued enrollment of up to approximately 20 additional subjects (total of 40 subjects per tumor type) (Stage 2) to obtain additional safety/efficacy data for the combination.

The safety, tolerability, and preliminary efficacy data from Stage 1 of the cohort expansion will be evaluated per tumor type and discussed by the sponsor with investigators prior to enrolling 20 additional patients during Stage 2.

Efficacy criteria for moving to Stage 2:

A minimum of 4 out of 20 subjects should demonstrate an objective response to study therapy. In general, if 0 to 3 responses are observed in a given tumor specific cohort during Stage 1 of cohort expansion, Stage 2 will not be enrolled for that tumor type. Please note: Ongoing assessment of data from initial 20 patients may be used to consider additional enrollment in that tumor type at a later date (to consider the possibility of delayed responses).

An additional 50 treatment naïve PD-L1 negative melanoma subjects will be treated at MTD/HAD to further evaluate if there is an efficacy signal in this population. Additional subjects may be enrolled and treated so as to accrue a minimum of 50 evaluable subjects with at least 2 on treatment scans.

Safety criteria for moving to Stage 2:

If the rate of DLTs exceeds 33% in a given tumor type; the findings will be discussed by sponsor with investigators and further enrollment may be interrupted for that specific tumor type.

Safety data from subjects enrolled in Stage 1 of the expansion phase will be reviewed by BMS medical and safety teams, and discussed with and endorsed by participating investigators, prior to moving to Stage 2 of cohort expansion.

If the efficacy and safety data from a given tumor type meet the minimum criteria for moving forward, approximately 20 additional subjects will be enrolled during Stage 2 of cohort expansion. The evaluation of data from Stage 1 and the decision to begin Stage 2 of the expansion phase of the study can be made up to one year following completion of the enrollment of Stage 1 for each individual tumor type.

Dose Limiting Toxicity: DLTs are defined in Section 4.5.2. The incidence of DLTs which occur within 8 weeks following the start of study therapy will guide dose escalation decisions. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4).

For the purposes of subject management, drug-related AEs occurring at any time which meet the DLT definition will lead to dose interruption and or permanent discontinuation of study drug as defined in Sections 4.5.5 and 4.5.7.

Duration of Study: The total time on study for any individual subject is expected to be approximately 3.1 years. The total duration of the study is expected to be 4.5years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled.

Number of Subjects: Up to approximately 260 subjects will be dosed.

Study Population:

Subjects at least 18 years old, who have histologic confirmation of a solid malignancy or B-cell NHL that is advanced (metastatic and/or unresectable), with measurable disease will be eligible to participate in the study.

For Dose Escalation: Subjects with any solid tumor type (with the exception of primary central nervous system tumors) and B-cell NHL are eligible to enroll.

For Cohort Expansion: Subjects must have one of the following tumor types to be eligible: NSCLC; MEL, SCCHN, DLBCL, or FL.

- A fresh biopsy is required to determine PD-L1 status prior to treatment into the PD-L1 negative, treatment-naive melanoma cohort.

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

Study Drug for CA186107		
Medication	**Potency**	**IP/Non-IP**
Urelumab (BMS-663513)	5 mg/mL	IP
Nivolumab (BMS-936558)	10 mg/mL	IP

Study Assessments:

Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be assessed continuously during the study and for 100 days after the last treatment. Both AEs and laboratory tests will be graded using the NCI CTCAEv4.

Efficacy Measures:

- In solid tumor patients, disease assessment with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline and every 8 weeks until confirmed disease progression, at the completion of follow-up, or until subjects withdraw from the study. Tumor responses will be derived for appropriate populations of subjects as defined by RECIST v1.1 based on recorded tumor measurements (see Appendix 1).
- For lymphomas, the primary efficacy assessment is objective response rate (ORR), defined as a subject achieving either a partial remission (PR) or complete remission (CR) according to the revised International Working Group Criteria for non-Hodgkin Lymphoma (Revised Response Criteria for Malignant Lymphoma, Cheson BD, J Clin Onc,2007 Feb 10;25(5):579-86. Epub 2007 Jan 22, [Appendix 2]). The primary efficacy assessment, along with the secondary endpoints of duration of OR, complete remission rate (CR), and progression free survival (PFS) will be performed based on investigators assessments. Subjects will be assessed for response by imaging (spiral CT/MRI) beginning at week 8 and follow the schedule shown in Table 5.1-2 and Table 5.1-3 until disease progression. A PET scan is required to confirm CR. Subjects eligible for re-treatment will be assessed for response by imaging (spiral CT/MRI) beginning at week 8 and follow the schedule shown in Table 5.1-5 and Table 5.1-6 until disease progression.
- At the sponsor's discretion, scans and measurements may be collected and reviewed by independent radiologists at a later date, or at any time during the study.

Pharmacokinetic Measures: The nivolumab pharmacokinetic concentrations will be measured at specified time points to derive the PK parameters (Ceoinf, Ctrough, Cmax, Tmax, AUC [0-T], AUC[TAU]). Pharmacokinetic serum concentrations of urelumab will be measured at specified time points to derive PK parameters (Ceoinf, Cmax, Ctrough, Tmax, AUC[0-T], AUC[TAU]).

Immunogenicity Measures: Serum samples to evaluate development of positive anti-drug antibody (ADA) response to urelumab and nivolumab will be collected at specified time points.

Biomarker Measures: The sample collection and biomarker assessment strategy is designed to address the key questions listed below regarding the actions of urelumab and nivolumab and the simultaneous modulation of the innate and adaptive immune systems.

- Does concurrent blockade of the PD-1 pathway and costimulation with anti-CD137 agonistic antibody affect aspects of innate and adaptive immunity that lead to enhancement of clinical activity (versus activity previously observed using either agent alone)?
- Are there pre-treatment markers expressed in blood or tumor tissue (eg, PD-L1; CD137) that associate with clinical outcomes?
- Does the combination of CD137 agonism with PD-1 blockade enhance anti-PD-1- and/or anti-CD137-mediated pharmacodynamic effects (versus effects previously observed using either agent alone)?

[redacted]

- Separate whole blood samples (PAXgene) will be obtained at baseline and at multiple times during treatment to monitor pharmacodynamic changes in expression of immunoregulatory genes including immunoglobulins, interferon-inducible genes, and genes associated with major immune cell subtypes.

  Whole Blood - for PBMC-based cytometry: Cytometry will be used to assess baseline and serial on treatment alterations in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs).

  Serum: To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and/or safety of nivolumab-urelumab treatment, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be investigated by ELISA and/or other relevant multiplex-based protein assay methods.

Statistical Considerations:

Sample Size Determination:

Dose escalation: As this is a Phase 1/2 dose escalation trial, the sample size at each dose cannot be determined exactly, as it depends on the number of observed toxicities. Approximately 3 to 9 subjects are expected to be treated during dose escalation in each cohort, and up to 12 subjects may be dosed at selected cohorts.

Cohort Expansion:
Stage 1: During Stage 1 of the cohort expansion, approximately 20 subjects in each tumor type will be treated at the MTD/HAD dose level and schedule. With a sample size of approximately 20 subjects in each treatment regimen, it is intended to provide a general picture of the safety of each regimen. For example, if a low grade adverse event were observed in 3 or fewer patients, the 90% 1-sided upper confidence interval would be 30%.

Stage 2: During Stage 2 of cohort expansion, up to approximately 20 additional subjects will be treated in each tumor type. This will allow for further establishment of the safety profile of the combination and a preliminary assessment of efficacy. A total of 40 subjects (20 from Stage 1 and 20 from Stage 2) is based on achieving a higher precision. If in a cohort of 40 subjects 12, 15, or 18 responses are observed, then the lower limit of the one-sided 90% exact binomial CI for the ORR is 20%, 27%, and 34% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals. If the true ORR in a tumor type is 50%, then with 40 subjects in a tumor type there is 96% chance of observing at least 15 responses, and 87% chance of observing at least 17 responses, and there is 8% chance of observing 15 or fewer responses (false negative rate).

An additional 50 treatment naïve PD-L1 negative melanoma subjects will be treated at MTD/HAD to further evaluate if there is an efficacy signal in this population. Additional subjects may be enrolled and treated so as to accrue a minimum of 50 evaluable subjects with at least 2 on treatment scans. These 50 PD-L1 negative melanoma patients will be combined for analysis with approximately 18 PD-L1 negative melanoma patients from Cohort 2 for a total of 68 PD-L1 negative melanoma patients. Assuming an ORR of approximately 56%, a minimum of 38/68 responders would provide a 95% Clopper-Pearson confidence interval with a lower limit above 42%.

Endpoints:

Primary Endpoint: Safety as measured by the rate of adverse events (AEs) and serious adverse events (SAEs), is the primary endpoint of this Phase 1/2 study. All subjects who receive at least one (full or partial) dose of urelumab or nivolumab will be evaluated for safety during treatment and for up to 100 days in follow-up.

Secondary Endpoints:

- *Efficacy*: Best overall response (BOR), objective response rate (ORR), duration of response, and progression free survival rate (PFSR) will be assessed based on RECIST v1.1 in subjects with solid tumors, and based on investigator assessment per revised IWG criteria in subjects with lymphomas.
- *Pharmacokinetics*: Urelumab and nivolumab maximum concentration (Cmax [µg/mL]), end of infusion concentration (Ceoinf), time to maximum concentration (Tmax [hr]) trough concentration (Ctrough [µg/mL]) and area under the curve (AUC[0-T] and AUC[TAU] [µg.hr/mL]) will be evaluated using non-compartmental analysis in all treated subjects with adequate serum concentration data.
- *Immunogenicity*: Occurrence of specific ADA to urelumab and nivolumab will be determined.

[redacted]

Statistical Analysis:

Safety: All recorded adverse events will be listed and tabulated by system organ class, preferred term, tumor type, and treatment arm. The most current version of MedDRA will be used for coding. Vital signs and clinical laboratory test results will be listed and summarized by tumor type and treatment arm. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator; clinically significant abnormalities will be listed.

Pharmacokinetics: Summary statistics will be tabulated for the pharmacokinetic parameters by tumor type, dose, regimen, study day and time on urelumab PK subjects and nivolumab PK subjects where data is available. This data may also be pooled with other datasets for population PK analysis which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive ADA at any time point will be provided. The frequency of subjects with at least one positive ADA assessment, and frequency of subjects who develop ADA after a negative baseline assessment will be provided. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

Efficacy Analyses: Individual BOR, duration of response and PFS will be listed using RECIST v1.1 criteria in solid tumors and investigator assessed revised IWG criteria in lymphomas. BOR outcomes will be tabulated by tumor type and treatment arm. The ORR and PFS rate (eg, at 24 weeks) and the corresponding confidence interval will be provided by tumor type and treatment. The duration of response and PFS will be estimated by Kaplan-Meier methodology by tumor type, depending on data availability. PFS rates at 24 weeks will be similarly estimated, based on Kaplan-Meier methodology. Presentations of efficacy will include subjects in cohort expansion and subjects in dose escalation matching those in cohort expansion by tumor type and treatment. Individual changes in the tumor burden over time will be presented graphically within a tumor type. Landmark overall survival will also be assessed as part of exploratory efficacy analysis, by Kaplan-Meier plots and medians for each tumor type.

[redacted]

TABLE OF CONTENTS

Yervoy®(ipilimumab). In the largest survival analysis of the anti-CTLA-4 monoclonal antibody to date, patients receiving ipilimumab 22% of patients were alive at 3 years, no deaths being reported beyond 7 years and median 7-year overall survival was 17%.[9] Yet, 5-year survival rates for distant stage diseases are 15%,[10] and recurrent and/or metastatic malignant melanoma remains largely a fatal disease.[11] Moreover, only around 50% of patients carry the BRAFV600E mutation sensitive to targeted agents like Zelboraf®(vemurafenib), Debrafenib and Trametinib. With the recent health authority approvals of Opdivo and Keytruda for patients with metastatic melanoma, treatment options for patients who relapse following treatment with anti-PD-1 or anti-PD-L1 therapies will become increasingly important.

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer death in the US. In 2014, an estimated 224,210 new cases will be diagnosed, and 159,260 deaths are estimated to occur because of the disease accounting for 27% of all deaths due to cancer.[1] Most lung cancers (~ 80%) are non-small-cell lung cancers.[12] Of these patients, more than 65% present with locally advanced or metastatic disease.[13] Despite treatment with platinum- and taxane-based chemotherapy, patients with metastatic NSCLC have a median survival of approximately 12 months,[14] and a 5-year survival rate of approximately 15%.[15] Even though there has been an increase in the number of treatment options available for patients with NSCLC, there has been little overall survival (OS) improvement from several new agents such as pemetrexed, erlotinib and bevacizumab beyond very small subpopulations. Therapeutic options for mutation wild-type NSCLC are particularly limited after failure of front-line chemotherapy. Overall, this group of patients only has an OS of about 8 months after progression from platinum agents. Once resistance to tyrosine kinase inhibitors (TKIs) occurs, the patients who have EGFR mutations or ALK translocations will have a rapid disease progression. Therefore, the majority of NSCLC cases remain a disease with high burden and unmet medical need.Anti-PD-1 therapies have recently been approved by the US FDA and the European Medicines Agency (EMA) for the treatment of advanced NSCLC. With these recent approvals, patients who relapse following treatment with anti-PD-1 or anti-PD-L1 therapies will become an important new patient category which will require new treatment options.

Head and Neck Carcinoma Squamous Cell (SCCHN)

Head and neck cancer (HNC) is the sixth most common cancer, with a worldwide incidence of at least a half a million.[16,17] The vast majority of cases are squamous cell carcinoma of the head and neck (SCCHN), which account for 3% to 4% of all cancers in the US.[18,19] In 2013 in the United States, the American Cancer Society estimates 53,640 new cases are diagnosed and approximately 11,520 deaths due to this cause occur yearly.[20] HNCs describe malignancies of the upper aerodigestive tract which include squamous cell carcinomas (SCCHN) of the oral cavity, nasopharynx, pharynx and larynx. Smoking and tobacco products, alcohol use, and infection with human papillomavirus (HPV) are among the major risk factors, however, a shift in SCCHN epidemiology in recent decades has been observed. Tobacco- and alcohol-related disease has declined while HPV-driven malignancies have increased.[21] Approximately 10-20% of

recurrent/metastatic SCCHN is HPV+.[22,23] Epidemiological tracking of HPV-driven HNCs suggest that patients with HPV positive (HPV+) tumors have better response rates and survival after treatment.[24]

Treatment of recurrent or metastatic disease involves a multimodal approach including surgery, use of cytotoxic chemotherapies such as methotrexate, organoplatinum compounds, fluorouracil (5-FU), or taxanes, combination with the biologic agent cetuximab and radiation. Despite the availability of these multimodal and novel approaches in management, prognosis has been poor for patients with disease recurrence after therapy with curative intent, with median survival for patients with locoregionally recurrent or metastatic disease, treated with palliative chemotherapy alone, being only 8–10 months.[25] Metastatic or recurrent SCCHN remains an area of high unmet medical need and patients who progress after treatment (refractory or platinum-resistant disease) have the worst prognosis with median OS of 3 - 4 months and 1 year survival rate of < 5%.[26] In conclusion, there is no effective standard of care that provides survival benefits beyond 4 - 6 months in second line platinum refractory recurrent or metastatic SCCHN. New therapeutic options are needed for this patient group.

Diffuse Large B-Cell Lymphoma (DLBCL):

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults in the United States with a projected estimate of 22,390 new cases and almost 10,000 projected deaths in 2013.[27] With standard therapy, including rituximab (anti-CD20) and an anthracycline containing regimen, around 60-70% of patients are alive without lymphoma with a median follow-up of at least 4 years.[28] Therefore, despite improvements in overall survival of patients with DLBCL with the routine addition of rituximab, 30-40% of patients have disease that is either refractory to initial therapy or relapses after standard therapy.[29]

Relapsed/refractory DLBCL is treated with chemotherapy and rituximab but is a therapeutic option only in the approximately 50% patients who are eligible for intensive therapy. Those who are ineligible for an aggressive approach due to other co-morbidities, poor performance status, advanced age, or refusal are considered incurable. Of the patients eligible for high-dose chemotherapy, only 50% demonstrate chemosensitive disease such that they can go on to an autologous stem cell transplant (ASCT). About 50% of responders to a second chemotherapy regimen followed by ASCT maintain their response at 2 years.[30]

Treatment options following failure of ASCT are limited for patients with DLBCL. Optimal management strategies for these patients have yet to be established and outcomes for patients requiring subsequent lines of therapy post ASCT remain particularly poor.[31]

Patients who successfully undergo an ASCT still have an unacceptably high rate of disease recurrence. For non-transplant candidates who fail second line therapy or relapse post-transplant, therapy is palliative.[29] Without transplant, chemotherapy provides short-term disease control in relapsed/refractory DLBCL. Primary refractory subjects are unlikely to achieve CR with a second chemotherapy regimen and following relapse, a second remission is usually not durable. Therefore,

more effective therapies are needed in the relapsed/refractory setting and an agent or combination of agents that could overcome that subsequent refractory state could be a valuable new strategy in this population.

Follicular Lymphoma (FL)

FL is the second most common lymphoma in the United States and Western Europe, accounting for approximately 20% of NHL (overall) and the majority of low-grade lymphomas. In Europe, the incidence is 2.18/105 persons/year[32] and the median age at diagnosis of 60 years, slight female predominance (M:F ratio 1:1.7).[33] Conventional therapy for FL is not curative. Therefore, new, more effective therapies are needed. The safety and effectiveness of rituximab in relapsed, refractory Low-Grade or Follicular, CD20-Positive, B-Cell NHL were demonstrated in 3 single-arm studies enrolling 296 subjects. Despite the fact that most subjects respond to initial therapy (with ~ 40-80% CR),[34] depending upon the regimen used, and that rituximab has activity as a single agent, nearly all subjects later develop progressive disease. Also, up to 10% are refractory to their initial treatment. Therefore, new, more effective therapies that potentiate, and perhaps create more durable responses to rituximab, are needed.

CD137 (4-1BB) and Urelumab (BMS-663513)

CD137 (4-1BB or TNFRSF9), a TNF superfamily Type 1 membrane glycoprotein receptor, is expressed on the surface of lymphoid organs and can be detected on activated T cells (CD4+ and CD8+), activated NK cells, natural killer T (NKT) cells, regulatory T cells, activated thymocytes, intraepithelial lymphocytes and eosinophils.[35,36] CD137 is not detected on the surface of resting T and B lymphocytes or activated B lymphocytes.[37,38] CD137 expression has now also been reported on splenic, follicular, and GM-CSF-stimulated bone marrow (BM) dendritic cells (DC) as well as on BM derived mast cells and DCs.[39,40,41] The natural ligand for CD137 is designated as CD137L, a TNF superfamily Type II membrane glycoprotein.[42] CD137L is expressed on the surface of activated T lymphocytes, macrophages, monocytes, DCs and B lymphocytes. In addition to its role on effector cells, signaling through CD137 enhances the ability of CD137 positive DCs to potentiate T cell responsiveness to alloantigens.[43] More recent evidence suggests that CD137 expressed on tumor-associated endothelial cells play a role in augmenting T cell trafficking into tumors.[44]

Urelumab is a fully human agonistic mAb specific to the human CD137 receptor (4-1BB). Urelumab activates the CD137 pathway and provides a strong costimulatory signal to T cells and NK cells, resulting in enhanced cytokine production (chiefly IFNγ), survival and proliferation. Consequently, urelumab can enhance the function of antigen-specific T cells and mediate clinical antitumor activity by enhancing the host antitumor immune response.

Urelumab is the first agonistic anti CD137 antibody studied in humans. By the end of 2008, four studies in humans had been conducted using urelumab: 2 monotherapy studies (a Phase 1 study, CA186001, in subjects with solid malignancies and a Phase 2 study, CA186006, in subjects with advanced melanoma) and 2 phase 1 combination therapy studies [CA186004 (which

combined urelumab with carboplatin and paclitaxel in subjects with solid malignancies) and CA186005 (which combined urelumab with radiation and carboplatin plus paclitaxel in subjects with non small cell lung cancer)]. In total, 291 subjects including 273 subjects treated with monotherapy and 18 subjects treated on the combination trials have received urelumab treatment in these 4 studies. Hepatotoxicity, was the most frequent clinically important toxicity.

On 18-Nov-2008, a fatal case of drug-related hepatotoxicity was reported in a subject receiving urelumab monotherapy at a dose of 5 mg/kg administered every 3 weeks on study CA186006. A second case of fatal, drug-related hepatotoxicity was reported on 30-Nov-2008 in a subject with melanoma treated with urelumab at a dose of 1 mg/kg administered every 3 weeks. On 05-Dec-2008, the sponsor suspended treatment of subjects with urelumab on all ongoing studies at the time (CA186001, CA186004, CA186005, and CA186006).

Although a maximum tolerated dose (MTD) of urelumab administered intravenously on an every 3 week schedule was not formally defined during dose escalation studies, the subsequent evaluation of hepatoxicity observed across the program suggested that the occurrence and severity of hepatoxicity was substantially increased at doses ≥ 1 mg/kg. A urelumab dose of < 1 mg/kg (ie, 0.1 mg/kg or 0.3 mg/kg every 3 weeks) resulted in infrequent ≥ Grade 3 hepatotoxicity (ALT 0/41 [0%]; AST 1/41 [2.4%]; total bilirubin 0/41 [0%]), whereas a urelumab dose of > 1 mg/kg every 3 weeks resulted in more frequent ≥ Grade 3 hepatotoxicity (ALT 43/189 [22.8%]; AST 39/189 [20.6%]; total bilirubin 8/189 [4.2%]). The frequency and severity of hepatotoxicity reached a plateau at doses > 1 mg/kg. [Note: for consistency, subjects on a q 3 week schedule only are compared here]. Those results suggest the multi-treatment MTD is < 1 mg/kg administered every 3 weeks.

In addition, anti-tumor activity as well as pharmacodynamic activity was observed across a wide dose range of Urelumab (0.1 to 10mg/kg).

Based upon review of these prior findings and the rare incidence of hepatotoxicity at doses below 1 mg/kg (described above), the Food and Drug Administration (FDA) lifted the clinical hold on 30-Jun-2011 and now a new Phase 1 monotherapy study, CA186011, is currently enrolling subjects. This study is a dose-escalation study at the 0.1 mg/kg and 0.3 mg/kg doses exploring the safety, tolerability, pharmacokinetics (PK), and immunoregulatory activity of IV urelumab in subjects with advanced and/or metastatic solid tumors or relapsed/refractory B-cell NHL. Dose escalation for study CA186011 has been completed with both doses with no DLTs at either dose.

PD-1 (CD279) and Nivolumab (BMS-936558)

Programmed Cell Death 1 (PD-1) is a cell surface signaling receptor that plays a critical role in the regulation of T cell activation and tolerance.[45] It is a type I transmembrane protein and together with BTLA, CTLA-4, ICOS and CD28, comprise the CD28 family of T cell co-stimulatory receptors. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[46] It is also expressed on natural killer (NK) cells[47]. Binding of PD-1 by its ligands PD-L1 and PD-L2, results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objectives

To assess the safety and tolerability of urelumab given in combination with nivolumab and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination, in subjects with advanced (metastatic and/or unresectable) solid tumors and B cell lymphomas.

1.3.2 Secondary Objectives

The secondary objectives are as follows:

- To assess the preliminary anti-tumor activity of the combination of urelumab and nivolumab in subjects with advanced solid tumors and B cell lymphomas.
- To characterize the pharmacokinetics (PK) of urelumab and nivolumab when co-administered.
- To monitor immunogenicity of urelumab and nivolumab administered as combination therapy.

[redacted]

1.4 Product Development Background

Data for urelumab and nivolumab follows with additional data also available in the respective Investigator Brochures.

1.4.1 Pharmacology

Urelumab (BMS-663513)

Urelumab is a fully human agonist IgG4κ isotype monoclonal antibody specific to the human CD137 receptor. Urelumab has a molecular weight of 150 kDa. Antibodies to the human CD137 receptor do not cross-react with the murine receptor and vice-versa. Therefore, an anti-murine CD137 receptor antibody homolog, BMS-469492, was used for evaluation in murine tumor models. Both urelumab and BMS-469492 (mouse anti-CD137) are agonistic antibodies which do not block the interaction of CD137 with its ligand, CD137L. Both the human and the mouseanti-CD137 antibodies increase IFNγ secretion from T cells activated with anti-CD3 in an in vitro functional assay.

The functional effects of urelumab on human and monkey T cells and peripheral blood mononuclear cells (PBMC) were determined by measuring IFNγ production by human T cells or monkey PBMC from healthy donors that were stimulated with anti-CD3 antibody (0.5 - 1 μg/mL) ± anti-human CD137 antibodies. Urelumab demonstrated co-stimulatory properties yielding higher levels of IFNγ in human and monkey cells compared to controls (anti-CD3 +/ control IgG).

Endogenous CD137 provides a co-stimulatory signal to T cells which results in enhancement of T-cell survival, T-cell proliferation and cytokine synthesis. To determine whether urelumab agonist antibody could elicit these same biologic effects, human T cells stimulated with anti-CD3 ± urelumab at concentrations known to induce IFNγ synthesis were stained with annexin-V and propidium iodide to determine the number of live cells (Annexin-V/Propidium iodide negative) and with cyclin D2 to assay the cell cycle status of treated cells. Concentrations of urelumab ranging from 0.4 - 10 μg/mL resulted in an increase in the number of live cells by approximately 1.8 to 2-fold, and yielded a significant increase in the number of cyclin D2 expressing T cells by 2.5 to 3- fold), confirming the costimulatory effect of urelumab.

Nivolumab (BMS-936558)

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (KD = 3.06 nM) and a high degree of specificity, thus precluding binding to its ligands PD-L1 and PD-L2. Nivolumab does not bind other related family members, such as BTLA, CTLA-4, ICOS or CD28. Pre-clinical testing of nivolumab demonstrated that binding to PD-1 results in enhanced T cell proliferation and release of interferon-gamma (IFN-gamma) in vitro.

1.4.2 Toxicity

Urelumab (BMS-663513)

Intravenous administration of urelumab to monkeys at single doses up to 100 mg/kg (AUC(0-INF) 534,000 μg h/mL) or repeated doses up to 100 mg/kg (AUC ≤ 833,000 μg h/mL), every two weeks for up to 9 month, did not result in drug-related toxicity. In mice, the liver was identified as the

principal target organ with the murine homolog BMS-469492. The liver lesion occurred after single exposures to BMS-469492 at doses ≥ 0.2 mg/kg and was characterized as minimal to moderate subacute inflammation of the liver and hepatocellular necrosis. Alanine or aspartate aminotransferases (ALT or AST) were generally sensitive and specific markers of this injury. Based upon the results from investigative studies the liver lesion was consistent with local IFN-γ-mediated injury and likely represents a mechanism-related effect of CD137 modulation in mice. The NOEL for liver inflammation in mice was achieved following a single dose of BMS-469492 at 0.1 mg/kg. No therapeutic window for this toxicity exists in the mouse efficacy models. No liver toxicity was observed in the monkey studies with urelumab.

Multiple-dose administration of the murine homolog BMS-469492 in mice induced liver and skin toxicities. There was minimal to moderate chronic inflammation and hepatocellular single-cell necrosis, increased ALT and AST, and pigment within Kupffer cells. The severity of the reversible hepatotoxicity in mice did not progress with increasing dose level, increasing number of doses, or with different dose frequencies. The NOEL for liver inflammation with multiple-dose administration of BMS-469492 to mice was not determined. The hepatic toxicity was not exacerbated by co-administration of known inflammatory agents, such as lipopolysaccharide (LPS) or acetaminophen (APAP). Instead, pre-treatment with BMS-469492 showed a trend to prevent or dampen the acute centrilobular hepatocellular necrosis induced by APAP. For further details on these studies, please refer to the Investigator Brochure.

Nivolumab (BMS-936558)

Toxicology studies in cynomolgus monkeys revealed that nivolumab was well tolerated at doses up to 50 mg/kg given twice weekly for 27 doses. Drug related findings were limited to a reversible decrease in triiodothyronine (T3) by 28%, [redacted].

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[66] 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.

1.4.3 Clinical Pharmacology and Safety

Urelumab (BMS-663513)

Four studies in humans have been conducted using urelumab: 2 monotherapy studies (a Phase 1 study, CA186001, in subjects with solid malignancies and a Phase 2 study, CA186006, in subjects with advanced melanoma) and 2 combination therapy phase 1 studies [CA186004 (combining urelumab with carboplatin and paclitaxel in subjects with solid malignancies) and CA186005 (combining urelumab with radiation and carboplatin with paclitaxel in subjects with non small cell lung cancer)]. In total, 291 subjects including 273 subjects treated with monotherapy and 18 subjects treated on the combination trials have received urelumab treatment in these 4 studies.

Of the 273 subjects treated with urelumab in monotherapy studies, drug-related AEs were reported in 216 (79.1%) subjects. Drug-related ≥ Grade 3 AEs were reported in 75 (27.5%) subjects. The most frequently reported drug-related AEs (> 10% of subjects) were fatigue, increased AST (23.4%), increased ALT (22.7%), fatigue (22.7%), rash (18.3%), nausea (13.5%), pruritus (11.7%), pyrexia (11.3%), decreased appetite (11.3%), and diarrhea (11%). Other drug-related AEs included headache, decreased platelets, asthenia, neutropenia, febrile neutropenia, and thrombocytopenia.

A maximum tolerated dose of urelumab administered intravenously on an every 3 week schedule was not formally defined during dose escalation studies. On 18-Nov-2008, a fatal case of drug-related hepatotoxicity was reported in a subject receiving urelumab monotherapy at a dose of 5 mg/kg administered every 3 weeks on study CA186006. A second case of fatal, drug-related hepatotoxicity was reported on 30-Nov-2008 in a subject with melanoma treated with urelumab at a dose of 1 mg/kg administered every 3 weeks. On 05-Dec-2008, the sponsor suspended treatment of subjects with urelumab on all ongoing studies at the time (CA186001, CA186004, CA186005, and CA186006).

After review and presentation of data to the FDA showing the significantly improved hepatic safety profile at doses below 1 mg/kg versus that of doses at or above 1 mg/kg, the clinical hold was lifted in June 2011 and subjects are currently being treated at doses below 1 mg/kg. CA186011, the Phase 1 monotherapy study exploring doses of 0.1 mg/kg and 0.3 mg/kg, has completed the dose escalation portion with no DLTs at either dose.

A case of potential drug-induced liver injury (DILI) occurred in study CA186011 in a subject treated at 0.3 mg/kg dose.[53] Per guidance in that protocol, enrollment in the 0.3 mg/kg dose level was halted and 0.3 mg/kg urelumab was determined to exceed the MTD and the 0.1 mg/kg dose level was selected for expansion.

Evaluation of the safety data revealed that drug-related hepatotoxicity is the most frequent clinically significant drug-related AE experienced among subjects treated with urelumab and is dose and schedule dependent. Exposure response analysis revealed that the occurrence and severity of hepatoxicity may be correlated with exposure (Cavg) and is substantially increased at doses ≥ 1 mg/kg. Doses of urelumab < 1 mg/kg every 3 weeks resulted in a low frequency of ≥ Grade 3 hepatotoxicity [0 Grade 3 ALT and 1 Grade 3 AST (2.3%) of 44 subjects] whereas an urelumab dose of ≥ 1 mg/kg every 3 weeks resulted in more frequent ≥ Grade 3 hepatotoxicity [43 Grade ≥ 3 ALT (22.8%) and 39 Grade ≥ 3 AST (20.6%) of 189 subjects]. (see Figure 1.1.1-1).

Nivolumab (BMS-936558)

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 1,500 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs which may be numerically greater in subjects with NSCLC because in some cases it can be difficult to distinguish between nivolumab related and unrelated causes of

pulmonary symptoms and radiographic changes. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics and targeted therapies is being explored. Most studies are ongoing and as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab and ipilimumab in subjects with MEL. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with greater frequency.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested, up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low grade (grade 1 to grade 2) with relatively few related high grade (grade 3 to grade 4) AEs. Most high grade events were manageable with the use of corticosteroids or hormone replacement therapy for endocrinopathies. Management algorithms including the use of immunosuppressive agents, such as corticosteroids, infliximab, etc., are provided in Appendix 3. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

Nivolumab has demonstrated clinical activity in response evaluable subjects with a variety of solid tumor malignancies in the following studies:

1) completed Phase 1 single-dose (MDX1106-01): n = 37 subjects with prostate cancer, MEL, NSCLC, RCC, and CRC
2) ongoing Phase 1 multi-dose, dose escalation study with nivolumab monotherapy (CA209003/MDX1106-03): NSCLC n = 129, MEL n = 107, RCC n = 34 subjects
3) ongoing Phase 1b study with nivolumab in combination with ipilimumab (CA209004/MDX1106-04): MEL n = 82 subjects
4) ongoing Phase 1 study with nivolumab monotherapy or in combination with platinum-based chemotherapy or erlotinib (CA209012): NSCLC, monotherapy n = 20, combination therapy n = 77 subjects

In addition, monotherapy or combination trials with nivolumab are on-going for subjects with SCCHN,[67] HCC,[68] CRC[69], GBM[70], and NHL.[71,72]

Updated overall clinical experience for nivolumab is available in the current version of the Investigator's Brochure.[52]

1.4.3.1 Pharmacokinetics of urelumab and nivolumab

Urelumab (BMS-663513)

The CA186001 first-in-human study showed that over the dose range studied (0.3 mg/kg to 15 mg/kg), urelumab concentrations were quantifiable within approximately 0.5 hour and peak concentrations occurred between 1 and 5 hours. The CA186001 and CA186011 studies showed that at 0.1 and 0.3 mg/kg (the dose range to be tested in this study), the mean serum elimination

half-life of urelumab in subjects with solid malignancies was approximately 125-135 hours (5.2-5.6 days). Serum urelumab Cmax and AUC increased in proportion to dose when administered at 0.1 to 0.3 mg/kg.

Nivolumab (BMS-936558)

A single dose pharmacokinetic analysis of 39 subjects with cancer given nivolumab at 0.3, 1, 3, and 10 mg/kg revealed that the median T_{max} across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The pharmacokinetics of nivolumab were linear in the range of 0.3 to 10 mg/kg with dose proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity (AUC_{INF}), with low to moderate inter-subject variability observed at each dose level. The mean terminal elimination half-life of nivolumab was 17 to 25 days, which is consistent with the half-life of endogenous IgG4. Both the elimination and distribution of nivolumab were independent of the dose.

1.4.4 Immunogenicity of Urelumab

Data from previous studies indicate that the overall rates of immunogenicity in patients treated with urelumab range from 11% (CA186001) to 27% (CA186006).

1.5 Overall Risk/Benefit Assessment

Subjects who have advanced solid tumors or B-cell NHL have extremely poor prognosis with limited curative options as stated in Section 1.[29,31] Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, MEL and lymphomas among other tumors.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced, previously treated melanoma. The combination of nivolumab and urelumab has the potential for increased benefit compared to nivolumab monotherapy.

Nivolumab has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. Side effects of nivolumab therapy may include those associated with immune mediated activation, such as thyroiditis and transaminitis. In addition, < 1% subjects who developed pneumonitis have died. To mitigate risk to subjects management algorithms for nivolumab-related adverse events from prior collective nivolumab experience have been included (Appendix 3).

Pharmacodynamic evidence of biologic activity was noted with urelumab monotherapy doses ranging from 0.1 mg/kg to 10 mg/kg. Clinical anti-tumor activity was also noted in subjects treated at urelumab doses starting at a 0.1 mg/kg dose in the Phase 1 monotherapy studies. Among solid tumors, anti-tumor activity was manifested in both objective responses and stable disease. All objective responses were observed in subjects with melanoma, and subjects with RCC and ovarian cancer were noted to have stable disease.

In study CA186006, one subject with metastatic melanoma developed a complete response and 7 of 41 showed stable disease. The complete response seen at 0.1 mg/kg and similar stable disease rates at 0.1 mg/kg and 1.0 mg/kg in study CA186006 suggest that there is anti-tumor activity at the initial dose level of 0.1 mg/kg. The similar stable disease rates of 1.0 mg/kg q3w and 1.0 mg/kg

q6w in study CA186006 suggest that a less frequent dosing interval may not impact efficacy, but may improve the safety profile. Pharmacodynamic evidence of biologic activity was also observed across the same dose range. In hematologic malignancies, objective responses were observed in 10 subjects with B-cell NHL treated at 0.3 mg/kg, including one complete response based on preliminary data from CA186011 (Part 3 of cohort expansion).

Taken together, these data provide evidence for further evaluation of the potential benefit of urelumab in combination nivolumab in solid tumors and B-cell NHL (in particular patients with the DLBCL or FL subtypes of B-cell NHL).

Hepatotoxicity is the most frequent clinically significant drug-related AE experienced among subjects treated with urelumab and is dose and potentially schedule dependent. However, the risk of hepatotoxicity at doses being tested in the current study (flat dose of 8 mg) is expected to be very low (Sections 1.1.1 and 1.4.3). In a prior monotherapy study (CA186006), that evaluated a dose of 0.1 mg/kg of urelumab which correlates with 8 mg flat dose, only 1 event of drug-related ≥ Grade 3 AST elevation was noted in the 41 subjects treated at the 0.1 mg/kg dose, and no other Grade ≥ 3 hepatic events occurred at this dose. In addition, in the ongoing monotherapy study CA186011 (Part 4 initiated in May 2014) exploring the 0.1 mg/kg dose of urelumab, no hepatic DLTs were observed during the dose escalation period with this dose, and no ≥ Grade 3 hepatic events were noted in subjects subsequently dosed at 0.1 mg/kg urelumab (preliminary safety data).

The possibility exists that the combination of urelumab and nivolumab will be more hepatotoxic than urelumab monotherapy, but this is considered unlikely since nivolumab monotherapy has not been associated with any significant hepatotoxicity. However, since this is an experimental study, the study protocol has been designed to minimize the risk of potential synergistic hepatotoxicity or unanticipated adverse events as follows:

1) **Enrollment Criteria** (Section 3.3.1) have been strictly chosen to minimize inclusion of subjects with underlying potential for increased hepatotoxicity from urelumab. Subjects with disease characteristics that could predispose to higher risk of morbidity during conduct of the study ie, patients with history of any hepatitis [eg, alcoholic or non-alcoholic steatohepatitis (NASH), drug-related, auto-immune] will be excluded from participation.

   The safety monitoring plan will require weekly liver function tests (LFTs) including AST, ALT alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and total bilirubin during treatment with urelumab (Table 5.1-1), and weekly for the first 8 weeks following last treatment with urelumab (Table 5.1-3). As detailed in Section 5.3.1 and Hepatotoxicity management algorithm (Appendix 3):

   Management of LFT Elevations:

   - Subjects experiencing ≥ Grade 3 elevations in ALT, AST, or total bilirubin will be discontinued.
   - Subjects experiencing ALT or AST > 3x ULN with concurrent total bilirubin > 2x ULN and fulfilling Hy's law criteria will be discontinued. If 2 events of Hy's Law (ALT or AST > 3 X ULN and concurrent T Bili > 2 X ULN) occurs at any

point in the study the entire cohort and all cohorts above will be considered to exceed the MTD and no subject will receive further doses at or above that dose level.

- Subjects experiencing Grade 2 elevations in ALT, AST or total bilirubin will have the next planned dose delayed until ALT, AST, and total bilirubin resolve to ≤ Grade 1

2) **Hepatotoxicity management algorithm:** To mitigate risk to subjects who develop drug-related hepatotoxicity, specific guidelines and algorithm for management of hepatotoxicity (see Appendix 3), with links to online resources with a comprehensive listing of potentially hepatotoxic agents are included in this protocol.

Screening tests, and clinical and laboratory safety assessments will also be performed on an ongoing basis and monitored closely. In addition, the AEs and SAEs will be reviewed by the Medical Monitor/Study Director and the Pharmacovigilance group to look for trends and safety issues. It is possible that unforeseen, unknown, or unanticipated reactions may occur since urelumab is an investigational product.

In addition to the potential risk associated with administration of study drugs, there is also some risk associated with tumor biopsies, including bleeding, infection and pain. While there is no direct benefit to subjects who undergo these procedures, there is the distinct possibility that the data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors.

Preliminary data in 138 patients treated with urelumab and nivolumab as of the clinical cutoff date of 30-Sep-2016, revealed that the most frequent TRAE was fatigue (31%); grade 3/4 ALT/AST elevations (2%/2%) and TRAEs leading to discontinuation (6%) were infrequent. No treatment-related deaths were reported. Twenty-five of 124 evaluable patients treated with the combination had objective responses (melanoma, n=23; SCCHN, n=1, NSCLC, n=1). The ORR in melanoma was 50% (23/46) including 9/18 of subjects with PD-L1 negative tumors by IHC.

There remains a significant unmet need for curative options in the tumor types being evaluated in this study including PD-L1 negative melanoma where the objective response rate to anti-PD-1 monotherapy is ~30-35%. Overall, the data indicate a favorable benefit/risk profile for the evaluation of a combination of urelumab with nivolumab in this study since the availability of more effective therapies or combination of agents would be of great benefit to these patients with advanced cancer.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form(s) 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.

- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a 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.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

The consent form(s) 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. The first phase of the study will consist of a dose escalation assessment of the safety and tolerability of urelumab administered with nivolumab in subjects with advanced solid tumors or B-cell NHL. The second part of the study will include a 2-stage cohort expansion in multiple tumor types (MEL, NSCLC, SCCHN, DLBCL and FL). Expansion cohorts will be explored at the maximally tolerated dose (MTD), highest administered dose (HAD), or at an alternative dose/regimen as determined by the investigators and the sponsor. The eligibility for the selected tumor types for the cohort expansions are listed in Study Population (Section 3.3).

Subjects will complete up to four periods of the study (Screening, Treatment, Clinical/Safety Follow-up, Survival/Long-term Follow-up): The total time on study for any individual subject is expected to be approximately 3.1 years.

3.1.1 Screening Period

The screening period will last for 28 days. Screening period begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subject is enrolled using the Interactive Voice Response System (IVRS).

3.1.2 Treatment Period

The Treatment Period will consist of up to 6 treatment cycles. Each cycle is 8 weeks for a total of 48 weeks. Nivolumab will be given every 2 weeks; urelumab will be given every 4 weeks. Subjects

completing approximately 48 weeks of initial treatment with ongoing disease control (CR, PR or SD) will be followed to monitor the duration of their disease control and may be eligible for retreatment if their disease progresses within 12 months following treatment discontinuation (see Protocol Section 4.5.8 for retreatment).

Treatment cycles are comprised of 4 doses of nivolumab per cycle and 2 doses of urelumab per cycle. Nivolumab will be administered on Days 1, 15, 29, and 43 and urelumab will be administered on Days 1 and 29 of each treatment cycle depending on the treatment cohort. On days where both study drugs are given, nivolumab will be given first followed by urelumab at least 30 minutes after completion of the nivolumab infusion.

Following each treatment cycle, the decision to treat a subject with additional cycles of study therapy, up to a maximum of 6 cycles, will be based on tumor assessment (evaluation performed between Days 49 and 56 of each cycle and completed before the first dose in the next cycle). Tumor progression or response endpoints will be assessed using RECIST 1.1 criteria for solid tumors (Appendix 1) and revised International Working Group (IWG) Criteria for non-Hodgkin Lymphoma[73] (Appendix 2) for lymphomas. Treatment beyond initial investigator-assessed progression (either clinical or radiographic) is permitted only if the subject has an investigator-assessed clinical benefit and is tolerating study drug. Subjects with a response of unconfirmed PD, SD, PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of either: 1) completion of the maximum number of cycles, 2) confirmed PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy; or 5) the subject meets criteria for discontinuation of study therapy as outlined in protocol Sections 3.5 and 4.5.7. Individual subjects with confirmed CR (or a stable and confirmed PR which, in the investigator's opinion, represents the maximum expected benefit for the subject) will be given the option to discontinue study therapy prior to 12 months on a case by case basis after specific consultation and agreement between the investigator and BMS MM in settings where benefit/risk justify discontinuation of study therapy.

3.1.3 Clinical/Safety Follow-up

Subjects that discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Subjects must be followed for at least 100 days after the last dose of therapy. Follow-up visits should occur at Days 30, 60 and 100 (± 7 days) after the last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after the last dose to monitor for adverse events. All subjects will be required to complete the 3 clinical safety follow-up visits regardless of whether they start new anti-cancer therapy, except those subjects who withdraw consent for study participation.

3.1.4 Survival/Long-Term Follow-up

After completion of the Clinical/Safety Follow-up period, all subjects will then enter the Survival/Long-Term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of survival follow-up will be 3 years following the first dose of study drug.

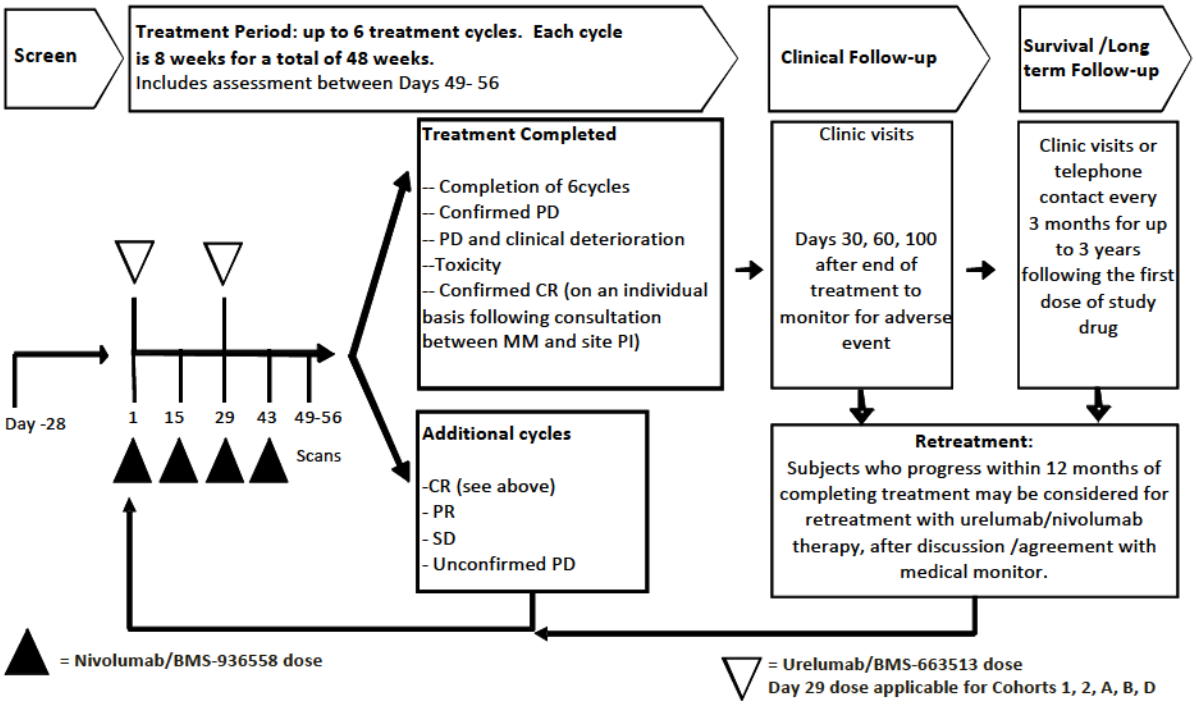
Subjects who discontinue study drug with ongoing SD, PR, or CR will continue to have tumor assessments completed every 12 weeks for the first year after discontinuation of study drug, and then continue to receive scans as per standard of care guidelines for follow-up or at a minimum of every 6 months up to 3 years following the first dose of study drug, or until disease progression or withdrawal of consent.

Subjects in the Survival/Long-term Follow-up period who have progression of disease will be allowed to receive tumor directed therapy as required.

Data from imaging assessments for subjects who have ongoing clinical benefit may continue to be collected after subjects complete the survival phase of the study.

A study schematic is presented below in Figure 3.1.4-1:

Figure 3.1.4-1: Study Schematic



CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

3.1.5 Dose Escalation

A 3+3+3 design will be used to assess the safety of urelumab given in combination with nivolumab. The cohorts for dose escalation are provided in Table 3.1.5-1. The Dose Limiting Toxicity (DLT) observation period will last for 8 weeks following the first dose of study medication. The DLT evaluation period will be defined as 8 weeks after administration of the first combination dose of nivolumab and urelumab, and includes subjects who have had administration

of at least one dose of nivolumab monotherapy during this interval. This interval is based upon inclusion of the earliest times to onset of clinically significant adverse events attributed to study drug, and also allows for a substantial amount of time for unexpected toxicities related to the dosing regimen to emerge.

Approximately three subjects will be treated initially at each dose regimen. In order to assure a sufficient number of evaluable subjects in each cohort an additional subject may be added to a cohort (ie, enroll a fourth subject in a cohort of 3). For example, if 4 subjects are treated in the cohort, the decision to enroll additional patients or escalate will be made after the 3rd evaluable patient completes the DLT window. In this situation, if the decision is made to remain at the same dose level and the 4th patient is evaluable, he/she will be included as part of the 2nd cohort at that dose level.

Note: (i) Should this action be taken, cohort tolerability assessment and subsequent dose escalation, if indicated, will occur when the minimum number of evaluable subjects required to assess tolerability have completed the 8 week DLT period. (ii) If any additional subject experiences an event that would, per protocol, result in either cohort expansion or the halting of dose escalation, the escalation rules as defined below in Table 3.1.5-2 will be followed.

Table 3.1.5-1: Dosages during Dose Escalation

Cohort	Total Subjects[a]	urelumab	nivolumab[b]
1	n = approximately 3-9	3 mg IV every 4 weeks	3 mg/kg or 240 mg IV every 2 weeks
2	n = approximately 3-9	8 mg IV every 4 weeks	3 mg/kg or 240 mg IV every 2 weeks
Total	n = approximately 6-18		

[a] 3-9 subjects will be enrolled during dose escalation. Additional subjects may be added to each dose level for a total of up to 12 subjects per dose level

[b] Nivolumab 3 mg/kg will be administered for subjects enrolled prior to Revised Protocol 02. Nivolumab 240 mg flat dose administered for subjects enrolled after Revised Protocol 02.

After dose escalation to the next cohort, 3-9 additional subjects may be enrolled in any previously tolerated (as defined by the dose escalation decision rules in Table 3.1.5-2) dose level (original 3-9 subjects from dose escalation plus additional subjects required to have a total cohort size of 12). If the rate of DLTs exceeds 33% in a given treatment regimen, the findings will be discussed and further enrollment may be interrupted for that specific treatment regimen and tumor type.

If one of the planned dose cohorts is determined to exceed the MTD, and/or based on ongoing safety/tolerability experience through the dose escalation phase of the study, an alternate dose escalation schema as outlined in Table 3.1.5-3 may be explored in consultation and agreement between the Sponsor and investigators.

Sentinel Subject: During dose escalation, the first subject treated at each dose level will receive C1D1 (eg, the first dose of study drugs) and will be observed for 3 weeks such that one combination dose followed by one nivolumab dose are administered before additional subjects in the cohort receive the first dose of study drug (ie, C1D1).

Dose Escalation Rules: Table outlines the decision rules for dose escalation based on the number of subjects and observed DLTs. No intra-subject dose escalation or reduction is allowed. Subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same dose level/regimen. Dose escalation will be based on the number of dose limiting toxicities (DLTs) experienced during the DLT observation period.

If dose escalation is terminated, then the dose or dosing regimen below that which invoked the stopping rule will be declared the MTD.

Table 3.1.5-2: Decision Rules During Dose Escalation

Number of Evaluable Subjects/ Cohort	**3-4[a]**			**6-8**			**9-12**	
Total Number of Observed DLTs	0	1	2 or more	1	2	3 or more	2	3 or more
Decision Rule	Dose Escalate	Enroll additional subjects in cohort to reach at least 6 subjects	Dose exceeds MTD	Dose Escalate	Enroll additional subjects at in cohort to reach at least 9 subjects	Dose exceeds MTD	Dose Escalate	Dose exceeds MTD

[a] If 4 subjects are enrolled in a cohort, the decision to enroll additional patients or escalate will be made after the 3rd evaluable subject completes the DLT window. In this situation, if the decision is made to remain at the same dose level and the 4th subject is evaluable, he/she will be included as part of the 2nd cohort at that dose level

If either Cohort 1 or Cohort 2 exceeds the MTD, alternate treatment regimens may be explored during dose escalation or cohort expansion (listed in Table 3.1.5-3).

Table 3.1.5-3: Alternate Treatment Regimens

Cohort Designation	**urelumab**	**nivolumab[a]**
A[b]	8 mg IV every 8 weeks	3 mg/kg or 240 mg IV every 2 weeks
B[b]	8 mg IV every 8 weeks	1 mg/kg or 80 mg IV every 2 weeks
C	3 mg IV every 4 weeks	1 mg/kg or 80 mg IV every 2 weeks

Table 3.1.5-3: Alternate Treatment Regimens

Cohort Designation	urelumab	nivolumab[a]
D[b]	3 mg IV every 8 weeks	3 mg/kg or 240 mg IV every 2 weeks

[a] Nivolumab 1 mg/kg or 3 mg/kg will be administered for subjects enrolled prior to Revised Protocol 02. Nivolumab 80 mg or 240 mg flat dose administered for subjects enrolled after Revised Protocol 02

[b] Dosing regimen not applicable following Revised Protocol 03 (Dated 31-Aug-2015)

All available clinical and laboratory data observed during dose escalation will be reviewed to determine the alternative treatment regimen listed in Table 3.1.5-3 to be evaluated. The nature, time of onset, and time to resolution of DLTs observed will be reviewed in the context of the current safety data from the respective urelumab and nivolumab trials. After review of this data, and after consultation between the investigators and the sponsor, the identified alternative treatment regimens may be evaluated.

3.1.6 Cohort Expansion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy and pharmacodynamic information regarding the combination of urelumab and nivolumab. Once the safety profile of all doses tested has been characterized and the MTD of combined administration of urelumab and nivolumab has been defined, cohort expansions will be initiated at the MTD, the HAD, or an alternate dose, if recommended by the investigators and the sponsor. Treatment doses in the cohort expansion groups will not exceed the HAD. The cohort expansion phase will follow a 2-stage design as outlined below in Table 3.1.6-1.

Table 3.1.6-1: Cohort Expansion

Tumor Types	Stage 1 Expansion	Stage 2 Expansion
Non-small Cell Lung Cancer (NSCLC)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 additional subjects
Melanoma (MEL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 additional subjects
Head and Neck Squamous Cell Carcinoma (SCCHN)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 additional subjects
Diffuse Large B Cell Lymphoma (DLBCL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 additional subjects
NSCLC (progressive or recurrent disease during or after anti-PD-1/anti-PD-L1 therapy)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects

Table 3.1.6-1: Cohort Expansion		
Tumor Types	**Stage 1 Expansion**	**Stage 2 Expansion**
Follicular Lymphoma (FL)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Melanoma (progressive or recurrent disease during or after an anti-PD-1/anti-PD-L1 containing treatment regimen)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects
Melanoma PD-L1 negative	Up to approximately 50 subjects at MTD or HAD	

3.1.6.1 Stage 1 Cohort Expansion

Stage 1 of the expansion phase will treat 20 subjects per tumor type at the MTD or HAD as identified during dose escalation followed by continued enrollment of up to approximately 20 additional subjects (total of 40 subjects per tumor type) (Stage 2) to obtain additional safety/efficacy data for the combination. The safety, tolerability, and preliminary efficacy data from Stage 1 of the cohort expansion will be evaluated per tumor type and discussed by the sponsor with investigators prior to enrolling 20 additional patients during Stage 2.

Efficacy criteria for moving to Stage 2:

In order to enroll additional patients in Stage 2 of cohort expansion a minimum of 4 out of 20 subjects in the first stage of cohort expansion need to demonstrate an objective response to study therapy. In general, if 0 to 3 responses are observed in a given tumor specific cohort during Stage 1 of cohort expansion, Stage 2 will not be enrolled for that tumor type. Please note: Ongoing assessment of data from the initial 20 patients may be used to consider additional enrollment in that tumor type at a later date (to consider the possibility of delayed responses).

An additional 50 treatment naïve PD-L1 negative melanoma subjects will be treated at MTD/HAD to further evaluate if there is an efficacy signal in this population. Additional subjects may be enrolled and treated so as to accrue a minimum of 50 evaluable subjects with at least 2 on treatment scans.

Safety criteria for moving to Stage 2:

If the rate of events that would qualify as DLTs exceeds 33% for a particular tumor type; the findings will be discussed by sponsor with investigators and further enrollment may be interrupted for subjects with that tumor type.

Safety data from subjects enrolled in Stage 1 of the expansion phase will be reviewed by BMS medical and safety teams, and discussed with and endorsed by participating investigators, prior to moving to Stage 2 of cohort expansion.

If the efficacy and safety data from a given tumor type meet the minimum criteria for moving forward, approximately 20 additional subjects will be enrolled during Stage 2 of cohort expansion. The evaluation of data from Stage 1 and the decision to begin Stage 2 of the expansion phase of the study can be made up to one year following completion of the enrollment of Stage 1 for each individual tumor type.

In the instance of unforeseen toxicity in a single expansion cohort, BMS will review the aggregate safety data both within a tumor type and across tumor types to determine if all subjects should have the dose reduced or treatment modified, or if the reduction should apply to only the specific tumor type. A decision on the impact of toxicity in one tumor-specific cohort across the program will be made based on the nature and severity of toxicity and feedback from participating investigators

3.1.6.2 Stage 2 Cohort Expansion

To evaluate additional safety, tolerability, and preliminary efficacy of the combination of urelumab and nivolumab, up to approximately 20 additional subjects will be enrolled following evaluation of the data from Stage 1 of Cohort Expansion.

3.2 Post Study Access to Therapy

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

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1.

No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The subject must sign the informed consent form prior to the performance of any study-related procedures that are not considered part of standard of care.

2) Target Population

a) Subjects must have histologic or cytologic confirmation of a malignancy that is advanced (metastatic and/or unresectable):

i) Dose Escalation:

(1). All solid tumor and B-cell NHL histologies will be permitted during dose escalation, except for subjects with primary CNS tumors, CNS lymphoma or with CNS metastases as the only site of active disease.

(2). Subjects must have received and then progressed, or been intolerant to, at least one standard treatment regimen in the advanced or metastatic setting, if such a therapy exists. Subjects who refuse or are ineligible for standard therapy will be allowed to enroll provided their refusal/ineligibility is documented in medical records.

ii) Cohort Expansion

(1). The following tumor types will be permitted during cohort expansion:

a. Non Small Cell Lung Cancer (NSCLC). No prior anti-PD-1/anti-PD-L1 therapy

i. Must have recurrent or progressive disease during or after platinum doublet-based chemotherapy for advanced or metastatic disease OR must have recurrent or progressive disease within six months after completing platinum-based chemotherapy for local disease.

ii. Subjects with non-squamous histology must have known EGFR and ALK status.

iii. Subjects with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor.

iv. Subjects with an ALK translocation must have received an ALK inhibitor.

b. Melanoma(MEL)

i. Not applicable.

ii. Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period.

iii. Histologically confirmed unresectable Stage 3 or Stage 4 melanoma as per American Joint Committee on Cancer (AJCC) staging system

iv. Treatment naive subjects (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma).

1. Note: Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 4 weeks or 5 half-life times (whichever is shorter) prior to randomization and all related adverse events have either returned to baseline or stabilized.

c. Head and Neck Squamous Cell Carcinoma (SCCHN)

i. Histologically confirmed incurable locally advanced, recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

ii. Confirmation of tumor HPV status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.

iii. Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper

measurement (eg, superficial skin lesion as per RECIST 1.1) or a lesion that has been visualized and photographically recorded with measurements and shown to have progressed.

iv. Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

d. Tumor Biopsy confirmation of relapsed or refractory DLBCL, or transformed lymphoma (TL), prior to the initiation of study drug.

i. TL is limited to DLBCL. Subjects with Grade 3b follicular lymphoma are excluded.

ii. DLBCL or TL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.

iii. Documentation of the above should be present in the subject's medical record.

iv. Prior treatment as defined below;

1. Subjects with relapsed DLBCL or TL after high-dose conditioning chemotherapy and ASCT, or
2. Subjects with relapsed or refractory DLBCL or TL after at least 1 prior multi-agent chemotherapy regimen if ASCT ineligible. Ineligibility for ASCT will be determined using local institutional criteria.

<u>Definition of Relapsed DLBCL</u>

- the appearance of new lesions > 6 months after obtaining a CR
- an increase ≥ 50% in the size of previously involved sites > 6 months after completing planned therapy

<u>Definition of Refractory DLBCL</u>

- < 50% decrease in lesion size after planned therapy,
- the appearance of new lesions during therapy or < 6 months after completion of planned therapy
- an increase of ≥ 50% in the size of previously involved sites during therapy or < 6 months after completion of planned therapy.

v. Measurable disease: Subjects must have at least one lesion that is > 15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions per computed tomography (spiral CT) or MRI

e. Non Small Cell Lung Cancer (NSCLC).Subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy:

i. Must have received platinum based chemotherapy for advanced or metastatic disease; or locally advanced disease

ii. A minimum of 5 subjects in Part 1 of Cohort Expansion should have squamous histology

iii. Subjects with non-squamous histology must have known EGFR and ALK status.

iv. Subjects with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor.

v. Subjects with an ALK translocation must have received an ALK inhibitor.

vi. Must have received anti-PD-1/anti-PD-L1 treatment as most recent therapy and have progressed during or after therapy.

vii. The last dose of prior anti-PD-1/anti-PD-L1 treatment ≥ 28 days from initiation of study therapy.

viii. No more than 25% of NSCLC subjects (5 during stage 1 and 5 during stage 2 of cohort expansion) will be enrolled with primary refractory disease (ie, a BOR of PD per RECIST v1.1). The remaining subjects in the cohort will be subjects with relapsed disease (ie, SD, PR or CR but progressing on therapy).

f. Follicular Lymphoma (FL)

i. Tumor biopsy confirmation of relapsed or refractory FL must be obtained prior to the initiation of study drug.

1. Grade 1, 2, or 3a FL without pathologic evidence of transformation.
2. FL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.
3. Documentation of the above should be present in the subject's medical record.
4. Treatment of FL consisting of ≥ 2 prior treatment lines; each of the 2 prior treatment lines must include CD20 antibody and/or an alkylating agent (eg, bendamustine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, busulfan, nitrosoureas). At least one of the prior treatment lines must include rituximab.

   NOTE: Separate lines of therapy are defined as 2 regimens separated by disease progression, relapsed disease, or refractory disease.

ii. Definition of Relapsed FL

1. The appearance of new lesions > 6 months after obtaining a CR
2. An increase ≥ 50% in the size of previously involved sites > 6 months after completing planned therapy.

iii. Definition of Refractory FL

1. < 50% decrease in lesion size after planned therapy
2. The appearance of new lesions during therapy or < 6 months after completion of planned therapy
3. An increase of ≥ 50% in the size of previously involved sites during therapy or < 6 months after completion of planned therapy

g. Melanoma (MEL) Subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy:
   i. Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period.
   ii. Histologically confirmed unresectable Stage 3 or Stage 4 melanoma as per American Joint Committee on Cancer (AJCC) staging system
   iii. Must have received anti-PD-1/anti-PD-L1 with or without anti-CTLA4 treatment as most recent therapy and have progressed during or after therapy.
   iv. The last dose of prior anti-PD-1/anti-PD-L1 treatment ≥ 28 days from initiation of study therapy.
   v. No more than 25% of MEL subjects (5 during stage 1 and 5 during stage 2 of cohort expansion) will be enrolled with primary refractory disease (ie, a BOR of PD per RECIST v1.1). The remaining subjects in the cohort will be subjects with relapsed disease (ie, SD, PR or CR but progressing on therapy).

h. Melanoma (MEL) Subjects with PD-L1 negative
   i. Fresh, pre-treatment biopsies are required.
   ii. Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period.
   iii. Histologically confirmed unresectable Stage 3 or Stage 4 melanoma as per American Joint Committee on Cancer (AJCC) staging system
   iv. Treatment naive subjects (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma).
      1. Note: Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 4 weeks or 5 half-life times (whichever is shorter) prior to randomization and all related adverse events have either returned to baseline or stabilized. However, no prior therapy with immune checkpoint inhibitors (eg, anti-PD-1, anti-PD-L1, anti LAG 3 and anti-CTLA4); immune costimulatory molecules (eg, anti-CD137, anti-OX40, anti GITR); anti-cancer vaccines (eg, Provenge, MAGE-3); or other immune modulating monoclonal antibodies is permitted.
   v. Subjects must be PD-L1 negative (PD-L1 tumor cell expression <1%) based on IHC testing performed by a BMS selected vendor on a fresh tumor sample collected during the screening period.

b) Presence of at least one lesion with measurable disease, which is distinct from the biopsy lesion, as defined by RECIST v1.1 for solid tumors or revised IWG criteria for B-cell NHL for response assessment. The only exception permissible is in sole accessible, bulky DLBCL lesions that are > 5 cm in largest diameter. Lesions meeting this criterion can be

biopsied and followed as an index lesion. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

c) Subjects must consent to allow the acquisition of existing formalin-fixed paraffin-embedded (FFPE) material, either a block or at least 10-15 unstained slides, for performance of correlative studies:
   i) For NSCLC (no prior anti-PD-1/anti-PD-L1), tissue must have been collected within 6 months of trial entry.
   ii) For other solid tumor types, tissue may have been collected at any time prior to first dose of study drug.
   iii) The solid tumor tissue specimen must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review and randomization. Note: For DLBCL and FL subjects *only*, FNA specimens are mandatory. FNA specimens may be omitted only in cases where a portion of the excisional biopsy specimen will be available for protocol-specified cytometry assessments (See Section 5.7.2). Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable
   iv) For subjects with no available archived specimen, a fresh tumor biopsy may be collected to fulfill this criterion.
   v) For subjects with NSCLC (relapsed/refractory to prior anti-PD-1/anti-PD-L1), tissue must have been collected after progression from prior anti-PD-1/anti-PD-L1.
d) The first 20 subjects with MEL and SCCHN in the Stage 1 of the expansion will be required to undergo mandatory pre-treatment and on-treatment biopsies in the cohort expansion phase at acceptable clinical risk as judged by the investigator. Biopsies in the MEL and SCCHN cohorts must be excisional, incisional, or core needle biopsies. The biopsy lesion must be distinct from a target lesion.
e) All subjects in the DLBCL and FL expansion cohorts will be required to undergo mandatory pre-treatment biopsies and the first 20 subjects in Stage 1 of the expansion phase will be required to undergo mandatory on-treatment biopsies with adequate tissue collection to perform specified analyses. The biopsy lesion must be distinct from an index lesion. Note: The only exception permissible is in sole accessible, bulky lesions that are > 5 cm in largest diameter. Lesions meeting this criterion can be biopsied and followed as an index lesion.
f) ECOG status of 0 or 1.
g) Adequate organ function for subjects with solid tumor histologies as defined by the following (institutional levels of lab normal values based on ethnicity will be allowed for WBC, ANC, and Hemoglobin):
   i) WBC ≥ 2000/μL (stable off any growth factor within 4 weeks of first study drug administration)
   ii) Neutrophils ≥ 1500/μL (stable off any growth factor within 4 weeks of first study drug administration)

iii) Platelets ≥ $100x10^3/\mu L$ (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

iv) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

v) Creatinine ≤ 1.5x ULN

vi) ALT and AST ≤ 3x ULN

vii) Total bilirubin ≤ 1.5x ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin)

viii) Normal thyroid function, subclinical hypothyroidism (TSH < 10 mIU/mL) or have controlled thyroid disorder

h) Adequate organ function for subjects with B-cell NHL malignancies as defined by the following:

i) Absolute Neutrophil Count ≥ 750/μL (no WBC growth factors for prior 14 days)

ii) Platelets ≥ 50 $x10^3/\mu L$ (no platelet transfusions for prior 14 days)

iii) Hemoglobin > 8.0 g/dL (no RBC transfusions for prior 7 days)

iv) Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

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

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

v) AST/ALT ≤ 3 x ULN

vi) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's Syndrome, who can have total bilirubin < 3.0 mg/dL).

i) Ability to comply with treatment, PK and PD sample collection, and required study follow-up.

3) Age, Sex, and Reproductive Status

a) Males and Females, ≥ 18

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks 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 study drug(s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 31 weeks 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 two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female condom*

* A male and female condom must not be used together

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected central nervous system (CNS) metastases or with the CNS as the only site of disease are excluded. Subjects with CNS lymphoma are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. Please note: for SCCHN subjects with direct extension of tumor through the base of skull will not be excluded as they are considered distinct from hematogenously spread parenchymal brain metastasis.

b) Ocular melanoma

c) Participation in any prior clinical study with ipilimumab, or with nivolumab including subjects in comparator arms, in which overall survival is listed as the primary or co-primary endpoint and which has not completed analysis based on the primary endpoint. Exception: I-O experienced NSCLC and melanoma cohort (prior antibody therapy of anti-CTLA-4 and/or anti-PD-1 or anti-PDL-1).

d) Subjects who have received nivolumab are not eligible to be enrolled with the exception for those NSCLC and MEL subjects enrolling in the expansion cohorts where prior anti-PD-1 or anti-PD-L1 therapies are specifically required.

2) Medical History and Concurrent Diseases

a) Subjects with a prior malignancy are excluded, except adequately treated basal cell or squamous cell skin cancer, localized prostate cancer, carcinoma in situ of the cervix, or in situ ductal or lobular carcinoma of the breast. Subjects with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

b) Prior organ allograft or allogeneic bone marrow transplantation

c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid patients with a history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to randomization), psoriasis not requiring systemic treatment, or conditions not expected to recur are permitted to enroll.

d) A known or underlying medical condition that, in the opinion of the investigator or sponsor, could make the administration of study drug hazardous to the subjects, or could adversely affect the ability of the subject to comply with or tolerate the study.

e) Uncontrolled or significant cardiovascular disease including, but not limited to any of the following:

   i) myocardial infarction or stroke/TIA within the past 6 months

   ii) uncontrolled angina within the past 3 months

iii) any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes)

iv) QTc prolongation > 480 msec

v) history of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion)

vi) requirement for daily supplemental oxygen therapy

f) History of any chronic hepatitis as evidenced by:

i) Positive test for hepatitis B surface antigen (HBsAg)

ii) Positive test for qualitative hepatitis C viral load (by PCR)

Note: Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

iii) History of alcoholic or non-alcoholic steatohepatitis (NASH), auto-immune hepatitis, or previous grade 3-4 drug-related hepatitis) or any form chronic liver disease will be excluded.

g) Evidence of active infection ≤ 7 days prior to initiation of study drug therapy (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry).

h) Evidence or history of active or latent tuberculosis infection including PPD recently converted to positive; chest x-ray with evidence of infectious infiltrate; recent unexplained changes in fever/chill patterns.

i) Any significant acute or chronic medical illness.

j) Any major surgery within 4 weeks of study drug administration.

k) Subjects who are unable to undergo venipuncture and/or to tolerate venous access.

l) Known current drug or alcohol abuse

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

3) Prohibited Prior Treatments and/or Therapies

a) Prior therapy with immune checkpoint inhibitors (eg, anti-PD-1, anti-PD-L1, anti-LAG-3); immune costimulatory molecules (eg, anti-CD137, anti-OX40, anti-GITR); anti-cancer vaccines (eg, Provenge, MAGE-3); or other immune modulating monoclonal antibodies. Prior anti-CTLA4 is permitted. Prior anti-PD-1/anti-PD-L1 therapy is permitted for the NSCLC cohort described in Protocol inclusion criteria 2(a)(ii)(1)(e) above.

b) Subjects who have received prior anti-CTLA4 therapy:

i) Prior anti-CTLA4 therapy within 100 days from the first day of study therapy.

ii) Subjects who have received prior anti-CTLA4 blockade and experienced the following immune-mediated adverse events:

(1). Grade 3 or > pneumonitis, hepatitis, colitis, ocular events;

(2). Any CNS event regardless of severity;

(3). Any immune-mediated adverse event requiring additional immunosuppressive therapy beyond steroids for management.

c) Any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, radiotherapy, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study drug administration, with the exception of GnRH agonist therapy for subjects with prostate cancer. Prior palliative or targeted radiotherapy must have been completed at least 2 weeks prior to the first dose of study drug.

d) Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to study drug. The use of the inactivated seasonal influenza vaccine (Fluzone®) is allowed.

e) Use of growth factors, including, but not limited to, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) or erythropoietin within 4 weeks prior to the first dose of study drug. Note: Subjects with DLBCL only: use of G-CSF or GM-CSF within 2 weeks prior to first dose of study drug (Section 3.3.1 2h(i)).

f) Use of pRBC or platelet transfusion within 2 weeks for solid tumors and 7 days for B-cell NHL prior to the first dose of study drug.

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

h) Chronic Obstructive Pulmonary Disease requiring recurrent steroids bursts or chronic steroids at doses greater than 10mg/day of prednisone or the equivalent

i) Subjects receiving RANK-L inhibitors or bisphosphonates are permitted. It is recommended that dosing of these agents begins at least 4 weeks prior to the expected first dose of study drug or after end of first cycle of treatment.

j) Use of any medicinal herbal preparations within 2 weeks prior to the first dose of study drug unless prescribed by the treating physician.

k) Subjects with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, Hormone replacement after adrenal crisis). Eligibility of subjects with prior ≥ Grade 3 checkpoint therapy-related immune adverse events, will be considered on a case-by-case basis after discussion with the MM (eg, asymptomatic isolated grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

l) Subjects who experienced prior non-life threatening checkpoint therapy-related immune-mediated adverse events must have confirmed recovery (resolve to baseline or Grade 1) from these events at the time of study entry, as documented by improvement of clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities.

4) Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at sites where mandated by local requirements.

b) Positive tests for hepatitis B virus surface antigen, hepatitis B core antibody, or hepatitis C RNA (Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

5) Allergies and Adverse Drug Reaction

a) History of allergy to components of urelumab or nivolumab, (eg, history of severe hypersensitivity reactions to drugs formulated with polysorbate 80).

6) Sex and Reproductive Status

a) Women who are pregnant or are breastfeeding.

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their 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 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.

[redacted]

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3.4.2.1 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating adverse events. Subjects receiving corticosteroids for treatment of drug-related adverse events must be at < 10 mg/day prednisone or equivalent prior to re-initiation of study therapy. Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Subjects receiving corticosteroid treatment for adverse events from prior immunotherapy must have completed steroid tapers for treatment of these adverse events by a minimum of 14 days prior to commencing treatment with study therapy.

Subjects may continue to receive hormone replacement therapy.

RANK-L inhibitors and bisphosphonates are permitted as clinically indicated but should be avoided, if possible, prior to completion of cycle 1.

Palliative and supportive care for disease related symptoms may be offered to all subjects on the trial after the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for subjects who have investigator assessed clinical benefit following consultation with the BMS Medical Monitor. Subjects should not receive study treatment during radiation or surgery.

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 and/or participation in the study;
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator indicates that continued participation in the study is not in the best interest of the subject;
- Termination of the study by Bristol-Myers Squibb (BMS);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness;
- Pregnancy;
- Documented and confirmed disease progression as defined by RECIST or IWG criteria (see Appendices 1 and 2) unless subject meets criteria for treatment beyond progression (See Section 3.5.1);
- Clinical deterioration while receiving active study therapy that in the opinion of the investigator indicates that continued participation in the study is not in the best interest of the subject;
- Discretion of the investigator;
- Inability to comply with the protocol requirements;
- Protocol defined reasons for discontinuation (see Section 4.5.7).

The investigator must notify the BMS Medical Monitor/designee in the event a female subject becomes pregnant within 24 hours and submit information to WWS on the pregnancy form within 24 hours. The study drug should be discontinued after pregnancy has been confirmed.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Table 5.1-3. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.5.1 Treatment Beyond Disease Progression

As described in Section 1.1.2 accumulating evidence indicates a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue on treatment beyond initial RECIST 1.1 defined PD, or progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) per 2007 IWG criteria, as long as they meet the following criteria:

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

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

3.5.1.1 Discontinuation due to further progression

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore must be included in the tumor burden measurement as follows:

For solid tumors: New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For B-cell NHL: New lesions are considered measurable at the time of initial progression if the long axis is more than 15 mm regardless of the short axis. If a lymph node has a long axis of 11 to 15 mm, it should only be considered measurable if its short axis is more than 10 mm.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be

considered to have investigator-assessed progressive disease at the time of the initial progression event.

3.5.1.2 Assessment schedule for the subjects with post-progression treatment

Subjects should continue to receive monitoring according to the On-Treatment Assessments in Table 5.1-2 and Table 5.1-5. Radiographic assessment by CT (preferred) or MRI described in Section 5.4 and Table 5.1-2 are required when subjects continue post-progression treatment. For subjects with B-cell NHL, study termination can be based on investigator-assessed evidence of clinical progression. FDG-PET scans for subjects with B-cell NHL are not mandated after investigator-assessed progression, but can be performed and results collected.

For subjects that discontinue post-progression treatment, no additional radiographic assessments will be required.

[redacted]

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

4 STUDY DRUG

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

- 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 (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

The study treatments include BMS-663513 and BMS-936558. Table 4-1 below indicates the dose level to be used for each panel.

Table 4-1: Treatment Administration

Cohort	Urelumab (BMS-663513)	Subjects Enrolled Prior to Revised Protocol 02	Subjects Enrolled After Revised Protocol 02
		Nivolumab (BMS-936558)	Nivolumab (BMS-936558)
1	3 mg IV every 4 weeks	3 mg/kg IV every 2 weeks	240 mg IV every 2 weeks
2	8 mg IV every 4 weeks	3 mg/kg IV every 2 weeks	240 mg IV every 2 weeks
A[a]	8 mg IV every 8 weeks	3 mg/kg IV every 2 weeks	240 mg IV every 2 weeks
B[a]	8 mg IV every 8 weeks	1 mg/kg IV every 2 weeks	80 mg IV every 2 weeks
C	3 mg IV every 4 weeks	1 mg/kg IV every 2 weeks	80 mg IV every 2 weeks
D[a]	3 mg IV every 8 weeks	3 mg/kg IV every 2 weeks	240 mg IV every 2 weeks

[a] Dosing regimen not applicable following Revised Protocol 03 (Dated 31-Aug-2015)

Product description and storage information is described in Table 4-2.

Expansion cohorts will be treated at the highest tested dose or a different dose level as selected by the sponsor.

For treatment visits where both BMS-663513 and BMS-936558 are administered, BMS-936558 will be administered first followed by BMS-663513 at least 30 minutes after completion of the BMS-936558 infusion. Detailed administration instructions will be provided separately via site training materials.

Table 4-2: Study Drugs for CA186107

Product Description Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
Urelumab (BMS-663513-01) Injection (for IV Infusion)	5 mg/ mL	IP	Open Label	3 mL fill in a 5 mL vial/ 1 vial/ carton A clear colorless to pale yellow solution which may contain particulates	Store refrigerated, 2° - 8° C, (36° - 46° F) Protect from Light, Protect from Freezing.
Nivolumab (BMS-936558-01) Injection, 100 mg/vial (10 mg/mL)	10 mg/mL	IP	Open Label	10 mL vial Box Clear to opalescent, colorless to pale yellow liquid. May contain light (few) particulates	Store 2-8 Degrees C (36-46 Degrees F); Protect from Light; Protect from Freezing Protect from Shaking.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

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) in a way different from 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: urelumab (BMS-663513) and nivolumab (BMS-936558).

4.2 Noninvestigational 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 noninvestigational products.

4.3 Storage and Dispensing

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

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

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

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

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.

Please refer to the current version of the Investigator Brochure/pharmacy reference sheets for complete storage, handling, and preparation information for BMS-663513 (urelumab) and BMS-936558 (nivolumab)

4.3.1 BMS-663513 (urelumab)

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 (eg, required diluents, administration sets).

As with all injectable drugs, care should be taken when handling and preparing urelumab. Whenever possible, urelumab should be prepared in a laminar flow hood or safety cabinet using standard procedures for the safe handling of intravenous agents applying aseptic techniques. Gloves are required.

If urelumab solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water.

Urelumab injection is an isotonic solution that may be diluted to concentrations between 0.05 mg/mL and 1 mg/mL using sterile disposable syringes prior to administration by IV infusion. Solutions of urelumab injection may foam; therefore, shaking and excessive agitation of vials should be avoided. Gentle swirling and inversion of the vials is recommended prior to dilution. The urelumab drug product solution may be diluted with 0.9% sodium chloride injection normal saline (NS), United States Pharmacopeia, in non-PVC/non-DEHP IV bags. The product must be infused using a volumetric pump at the protocol specific dose(s) and rate(s) through a sterile, non-pyrogenic, non-PVC/non-DEHP, IV infusion set containing a 0.2 µm polyethersulfone in-line filter. It is not to be administered as IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. The diluted solutions may be stored for up to 4 hours at ambient room temperature/room light, or for up to 24 hours in a refrigerator 2°C to 8°C (36°F to 46°F), but must be infused within each timeframe, respectively.

The infusion rates should be maintained at either 1.0 mL/min for the 60 minute infusion or at 0.5 mL/min if the rate has been reduced by half due to an infusion reaction. A minimum of 10 mL normal saline flush should be given at the end of the infusion. For convenience the infusion times and volumes for the various cohorts are listed below and should be used accordingly:

Dose escalation and dose expansion cohorts 8 mg or 3 mg dose per subject

- Infusion volume: 60 mL
- Infusion time: 60 min (1 mL/min)

Sample calculation for required volume of urelumab based on dose:

- Subject at 8 mg dose
- Total dose: 8 mg
- Volume urelumab: 8 mg / (5 mg/mL) = 1.6 mL

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.

4.3.2 BMS-936558 (nivolumab)

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on drug preparation, storage, handling and dispensing of nivolumab, please refer to the BMS-936558 (nivolumab) Investigator Brochure and/or pharmacy reference sheets.

Nivolumab is to be administered as a 60-minute IV infusion. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first followed by urelumab at least 30 minutes after completion of the nivolumab infusion. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the urelumab infusion.

Detailed administration instructions will be provided separately via site training materials.

4.4 Method of Assigning Subject Identification

CA186107 is an open label study. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to dosing. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003, ...00010. Those enrolled subjects meeting inclusion and exclusion criteria will be eligible to be treated and increasing sequentially with each additional enrolled subject. The subject number will be assigned by the Sponsor via Interactive Voice Response System (IVRS) once the subject signs the informed consent form. Each subject will then be identified by a distinct patient identification number (PID) which is comprised of the site number and the subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. The Investigator or designee will register the subject following the enrollment procedures established by BMS. The following information is required for registration:

- Date of birth
- Gender
- Date of Informed Consent
- Diagnosis (Expansion Phase only)
- Tumor Type (Expansion Phase only)

Enrolled subjects meeting all eligibility criteria will be assigned to a dose cohort.

Specific instructions for using IVRS will be provided to the investigational sites in a separate document.

4.5 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific dose level as listed in Table 4-1 in sequential order during dose escalation. Subjects in cohort expansion will be treated at the MTD, the HAD, or at an alternate dose, if recommended by the investigators and the sponsor.

Dosing calculations for nivolumab should be based on the body weight assessed at Day 1 per Table 5.1-1. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be re-calculated. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of nivolumab allowed once assigned. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.9.

Following implementation of revised protocol 02, nivolumab will be administered as flat dosing at the doses listed in Table 4-1.

Urelumab will be administered as flat dosing at the doses listed in Table 4-1.

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of study drug. See Section 4.5.9 for subsequent premedication recommendations following a nivolumab-related infusion reaction.

4.5.2 Dose Limiting Toxicities

Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (v4.0).

Non-hematologic Dose-Limiting Toxicity (DLT):

A. Hepatic Non-Hematologic DLT

Any one of the following study drug-related events will be considered a hepatic DLT:

- Any ≥ grade 3 elevation of AST, ALT or T bili
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase (ALP) (ie, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury or pDILI)*

*[Note that this special category of DLT uses ULN rather than CTC Grade for definition]

NOTE: Subjects who experience a DLT that is considered related only to urelumab may be allowed to continue nivolumab monotherapy following resolution of the event. This will be determined on a case by case basis, after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued treatment with nivolumab

monotherapy (eg, subjects with asymptomatic, isolated grade 3 ALT and/or AST elevation that responds rapidly to short 2-3 weeks course of steroid therapy).

B. Non-Hepatic Non-Hematologic DLT

Any of the following events will be considered a Non-Hepatic Non-Hematologic DLT:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 or greater non-dermatologic, non-hepatic non-hematologic study drug-related toxicity will be considered a dose-limiting toxicity with the following specific EXCEPTIONS:
    - Grade 3 or grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
    - Grade 3 nausea, vomiting or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention
    - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)

C. Dermatologic DLT

- Grade 3/4 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1-2 week infusion delay. Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

D. Hematologic DLT (study drug-related)

- Grade 4 neutropenia ≥ 7 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
- Grade ≥ 3 febrile neutropenia for 72 hours
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)
- Grade 4 anemia not explained by underlying disease

4.5.3 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration from adverse events caused by other therapeutic classes. Nivolumab and urelumab are 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
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The algorithms recommended for utilization in this protocol are included in Appendix 3.

4.5.4 Guidelines for Dose Modification

Intrasubject dose escalation or reduction of urelumab and nivolumab is not permitted in this study in order to allow better evaluation of extended safety and efficacy at individual dose levels and schedules.

4.5.4.1 Dose Reductions

No dose reductions of either urelumab or nivolumab are permitted in this study.

4.5.5 Dose Delays Due To Toxicity

Subjects who experience a DLT must have study drug held. Subjects who are required to permanently discontinue both study drugs are listed in Section 4.5.7. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological adverse events should be evaluated and managed per the toxicity management algorithms (Appendix 3). Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 4.5.6. Subjects eligible to resume study therapy will resume study therapy at the treatment visit following their last received study medication dose.

Depending on the dosing schedule (See Table 5.1-2 and Table 5.1-5), if there is a delay in dosing of combination dose (same day dose of urelumab and nivolumab) of between 1 -26 days (for subjects receiving the combination dose every 4 weeks), the procedures at the original scheduled visit should be performed as soon as possible. If the delay is more than 26, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent combination doses will follow at 4.

Depending on the dosing schedule (See Table 5.1-2 and Table 5.1-5), if there is a delay in dosing of nivolumab of between 1 -12 days, the procedures at the original scheduled visit should be performed as soon as possible. If the delay is more than 12 days, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent nivolumab doses will follow every 2 weeks.

Whereas the general guidance on dose delays as above will normally apply to all subjects, extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS Medical

Monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT drug-related adverse events, or experiences delays for management of a non-drug-related AE).

The end of cycle disease assessments (ie, CT/MRI, PET, etc) will continue on an every 8 weeks schedule relative to the subject's 1st dose regardless of any treatment delay incurred.

4.5.6 Criteria to Resume Treatment

Subjects experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 4.5.7 may resume treatment with study medication under the following criteria:

- Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value with the following exceptions:
  - Subjects may resume treatment in the presence of Grade 2 fatigue;
  - Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity;
  - Subjects with Grade 2 uveitis or eye pain or blurred vision not meeting DLT criteria (Section 4.5.2) must resolve to baseline prior to resuming study therapy;
  - Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed;
  - Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

NOTE: Subjects who experience a DLT that is considered related only to urelumab may be allowed to continue nivolumab monotherapy following resolution of the event. This will be determined on a case by case basis, after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued treatment with nivolumab monotherapy (eg, subjects with asymptomatic, isolated grade 3 ALT and/or AST elevation that responds rapidly to short 2-3 weeks course of steroid therapy).

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

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study sponsor. Any adverse event with clinical risk will be assessed on a case by case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

If treatment with study medication is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.7).

4.5.7 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue both study drugs for the following adverse events:

A. Any drug related AE occurring at any time that meets DLT criteria as outlined in Section 4.5.2 will require permanent discontinuation with the following **exceptions**:
   a) grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to grade 1 or baseline within 3 days with medical intervention;
   b) grade 3 pruritus or rash that returns to grade 1 or baseline within 7 days or baseline with medical intervention;
   c) grade 4 electrolyte abnormalities that < 72 hours in duration;
   d) grade 4 neutropenia ≤ 7 days in duration;
   e) grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis;
   f) grade 4 lymphopenia < 5 days in duration.

NOTE: Subjects who experience a DLT that is considered related only to urelumab may be allowed to continue nivolumab monotherapy following resolution of the event. This will be determined on a case by case basis, after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued treatment with nivolumab monotherapy (eg, subjects with asymptomatic, isolated grade 3 ALT and/or AST elevation that responds rapidly to short 2-3 weeks course of steroid therapy).

Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation with the following exceptions:

- Dosing delays 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.
- Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Whereas the general guidance on dose delays as above will normally apply to all subjects, extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs, or experiences delays for management of a non-drug-related AE). Tumor assessments should continue as per protocol even if dosing is delayed.

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 (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

4.5.8 Retreatment with Study Therapy

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study sponsor. Any adverse event with clinical risk will be assessed on a case by case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

Subjects who have completed all 6 cycles of treatment and who experience disease progression during the follow-up period after having experienced initial disease control (CR, PR or SD) within 12 months of last treatment with study therapy may be permitted re-initiation of study therapy at their original dose regimen after discussion and agreement with the BMS Medical Monitor. Subjects entering this phase will follow the Time and Events schedule as outlined in Table 5.1-4, Table 5.1-5, and Table 5.1-6. Samples for PK and ADA will be collected as per Table 5.5.1-3, select samples for PD (PBMCs, serum cytokine samples, flow panel samples) will be collected as outlined in Table 5.7-.

Subjects undergoing retreatment of study therapy should continue to meet the eligibility criteria with respect to laboratory parameters and organ function at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy.

Screening procedures that need to be repeated are outlined in Table 5.1-4. Subjects will continue to receive study therapy at the same dose levels as assigned at study start. Additional, separate, safety and efficacy listings will be presented for those subjects who reinitiated study therapy.

Subjects who achieve CR during initial therapy and chose to come off therapy for reasons other than toxicity, will be continue to be followed and will be allowed to be re-treated within 12 months of administration of last dose of study drug.

Subjects who experience DLT will not be eligible for retreatment, except as outlined in Section 4.5.2.

4.5.9 Treatment of Drug Related Infusion Reactions

Since nivolumab and urelumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.0 guidelines.

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

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

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

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

Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetominophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

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

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

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility. The investigator or their designated study personnel will maintain a log (Drug Accountability Log) of all study drugs received, dispensed and destroyed. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the sponsor.

4.8 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

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

Arrangements for the return of the study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures for initial treatment are presented in Table 5.1-1, Table 5.1-2, and Table 5.1-3. Study assessments for re-treatment are presented in Table 5.1-4, Table 5.1-5, and Table 5.1-6.

Table 5.1-1: Screening Procedural Outline (CA186107) - Initial Treatment

Procedure	Screening Visit (Day -28 to Day 1)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol- specific informed consent is signed. Contact IVRS to obtain study subject number. Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	
Medical History	X	Include any toxicity or allergy-related to previous treatments. Includes more detailed medical history of risk factors for potential events such as pulmonary-related events.
Tobacco and Alcohol History/Status	X	Document subject's history and current status of tobacco and alcohol use
Tumor tissue acquisition	X	**For patients with solid tumors (except for Melanoma PD-L1 negative cohort):** Tumors may be archival. 1 paraffin block or 10 - 15 FFPE unstained slides identified and shipped to the Central Lab prior to dosing. BMS Medical Monitor approval is required for subjects for whom tissue is not available. **For patients in the Melanoma PD-L1 negative cohort**: A fresh tumor biopsy is required. 1 paraffin block or 10 - 15 FFPE unstained slides to be shipped directly to the BMS selected vendor for testing prior to dosing.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 24 hours of dosing on Cycle 1 Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Performance Status	X	ECOG Performance Status (Appendix 4).
Physical Measurements	X	Includes height, weight.

Table 5.1-1: Screening Procedural Outline (CA186107) - Initial Treatment		
Procedure	**Screening Visit (Day -28 to Day 1)**	**Notes**
Vital Signs	X	Includes body temperature, seated blood pressure, heart rate and respiratory rate. Blood pressure, heart rate and respiratory rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation	X	Pulse oximetry collected at rest. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnosis pulmonary toxicity.
Revised International Prognostic Index (IPI) and Follicular Lymphoma International Lymphoma Index (FLIPI) at time of initial disease diagnosis	X	For subjects with B-cell NHL only. Refer to Appendix 5
Electrocardiogram (ECGs)	X	12-lead ECG; ECGs should be recorded after the subject has been supine for at least 5 minutes
Chest Radiograph	X	
Laboratory Tests		**Laboratory tests listed below must be completed within 2 weeks of Day 1 unless otherwise noted**
Chemistry (Excluding LFTs)	X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, fasting glucose, total protein, albumin, amylase, lipase, CRP, ferritin, uric acid, and LDH.
CBC w/differential & platelets	X	
LFT assessments	X	AST, ALT, alkaline phosphatase, total bilirubin, and GGT
Urinalysis	X	Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
PT/PTT	X	
Thyroid Function Tests (TFT)	X	TSH with free T3 and free T4

Table 5.1-1: Screening Procedural Outline (CA186107) - Initial Treatment		
Procedure	**Screening Visit (Day -28 to Day 1)**	**Notes**
Human Papillomavirus Status	X	SCCHN subjects only. Sites must submit and document prior HPV status within 28 days of dosing. For subjects with unknown status, tumor tissue will be required, per inclusion criteria. Subjects must consent to HPV testing.
Epstein-Barr Virus (EBV) Status	X	For subjects with B-cell NHL only. Sites must submit and document prior EBV status within 28 days of dosing. For subjects with unknown status, tumor tissue will be required, per inclusion criteria. Subjects must consent to EBV testing.
Document mutational status	X	Document EGFR and ALK for subjects with NSCLC. Document BRAF for subjects with MEL.
Document lymphoma risk classification	X	For subjects with B-cell NHL. May include, but are not limited to BCL2, MYC, BCL6, CD10, MUM1, Ki67, BCL2 14:18 translocation, and MYC break-apart.
Serology Tests	X	Within 28 days of dosing: Hep A IgM, Hep B surface antigen, Hep C antibody, Hepatitis C viral load Note: Testing for HIV-1, HIV-2 must be performed at sites where mandated by local requirements
Serum Pregnancy Test	X	WOCBP only **at screening and within 24 hours prior to dosing.** The serum pregnancy test may be completed on the first day of treatment provided the results are available before the start of study therapy. Minimum test sensitivity of at least 25 IU/L required.
FSH	X	Female ≤ 55 with amenorrhea to confirm menopausal status- See Section 3.3.3
[redacted]	[redacted]	[redacted]
Assessment of Signs and Symptoms	X	Collected for the period 2 weeks prior to Cycle 1 Day 1
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected starting at the time the subject signs informed consent and through 100 days post discontinuation of dosing or completion of the subject's participation in the study if the last scheduled visit occurs at a later time.

Table 5.1-1: Screening Procedural Outline (CA186107) - Initial Treatment		
Procedure	**Screening Visit (Day -28 to Day 1)**	**Notes**
Efficacy Assessments		
Diagnostic Imaging	X	CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X	Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases or who have not had brain imaging within 30 days of anticipated first study drug administration.
PET Scan	X	Required at screening for subjects with B-cell NHL only
Bone Scan	X	As clinical indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Clinical Drug Supplies		
Subject Registration via IVRS	X	

Table 5.1-2: On Treatment Procedural Outline (CA186107) - Initial Treatment

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Safety Assessments						
Targeted Physical Examination (PE)	X					A targeted (symptom-directed) physical examination performed by the investigator or designee is required at each subsequent visit.
Performance Status	X	X	X	X		ECOG score prior to dosing (Appendix 4)
Physical Measurements	X	X	X	X		Weight only prior to dosing
Vital Signs	X	X	X	X		Vital signs (body temperature, seated blood pressure, heart rate and respiratory rate) will be obtained before the BMS-936558 infusion, after the BMS-936558 infusion, before the BMS-663513, and after the BMS-663513 infusion. Subjects must be observed for 30 minutes after the BMS-663513 infusion before discharge. If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated. 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 examination, report changes on the appropriate non-serious or serious adverse event page. See Section 4.5.9 for treatment of infusion reaction.
Non-Serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 100 days after discontinuation of dosing. SAEs should be approved in TAO within 5 business days of entry
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Electrocardiogram (ECGs)	X					12-lead ECG (if performed on same day as study drug administration it is to be performed prior to dosing).

Table 5.1-2: On Treatment Procedural Outline (CA186107) - Initial Treatment

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Chest Radiograph						As clinically indicated.
Oxygen Saturation Levels	X	X	X	X		Collect pulse oximetry at rest prior to dosing.
Laboratory Tests	X	X	X	X		**On study labs (including pregnancy testing) to be done on site/local. Within 72 hrs prior to dosing**
Chemistry (excluding LFTs)	X	X	X	X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, CRP, ferritin, LDH.
CBC with differential & platelets	X	X	X	X		Should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7-1
LFT assessments	Weekly during treatment with urelumab and for 8 weeks following last urelumab dose then Days 1, D15, D29 and D43 of each subsequent cycle					Includes AST, ALT, total bilirubin, alkaline phosphatase and GGT. LFTs will be monitored weekly during treatment with urelumab and for 8 weeks following the last dose of urelumab
TFT	X					To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	X	X	X	X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy Serum or Urine Test for WOCBP	X	X	X	X		Urine or Serum within 24 hours prior to treatment, the minimum sensitivity of the pregnancy test must be 25 IU/L or equivalents of HCG. If pregnancy test is positive, subject must not receive study drug. Pregnancy test must be performed at a minimum of every 4 weeks in the event of dosing delays.
Sample Collection						
Pharmacokinetic (PK) Assessments						See Table 5.5.1-1

Table 5.1-2: On Treatment Procedural Outline (CA186107) - Initial Treatment

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Immunogenicity Assessments						See Table 5.5.1-1
Biomarker Assessments						See Table 5.7-1 and Table 5.7-2
Efficacy Assessments						
Diagnostic Imaging					X	By methods used at baseline. CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging					X	As clinically indicated
Bone Scan					X	As clinically indicated
PET Scan					X	Required to confirm a CR for subjects with B-cell NHL
Bone marrow aspirate and biopsy					X	Required to confirm CR in subjects with B-cell NHL with bone marrow disease at screening
Clinical Drug Supplies						
BMS-936558 Administration	X	X	X	X		
BMS-663513 Administration (Cohort 1, 2, C)	X		X			Cohort 1,2, C To start administration no sooner than 30 minutes after completion of the BMS-936558 infusion

Abbreviations: D = Day

[a] Day 1 of each cycle except where noted

Table 5.1-3: Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival/ Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
Safety Assessments					
Physical Examination (PE)	X	X	X		
Vital Signs	X	X	X		Includes body temperature, seated blood pressure, heart rate and respiratory rate. Blood pressure, heart rate and respiratory rate should be measured after the subject has been seated quietly for at least 5 minutes.
Performance Status	X	X	X		ECOG score (Appendix 4)
[redacted]	[redacted]	[redacted]			
Monitor for non-Serious Adverse Events	X	X	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 100 days after discontinuation of dosing. SAEs should be approved in TAO within 5 business days of entry of entry
Laboratory Tests					
Chemistry (excluding LFTs)	X	X	X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, CRP, ferritin, and LDH.

Table 5.1-3: Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival/ Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
CBC with differential & platelets	X	X	X		Should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7-1
LFT assessment	Weekly for 8 weeks following last urelumab (if applicable) and at 30 Day, 60 Day, 100 Day follow-up				LFTs will be monitored weekly for 8 weeks following the last dose of urelumab. Includes AST, ALT, total bilirubin, alkaline phosphatase and GGT
TFT	X	X	X		To include TSH with reflex testing (free T3 and free T4).
Urinalysis	X	X	X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy Serum or Urine Test For WOCBP	X	X	X		The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalents of HCG.
Sample Collection					
Pharmacokinetic (PK) Assessments	X	X	X		See Table 5.5.1-1
Immunogenicity (ADA) Assessments	X	X	X		See Table 5.5.1-1

Table 5.1-3: Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival/ Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
Efficacy Assessments					
Diagnostic Imaging			X	X	By method used at baseline. CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories. Subjects who discontinue the clinical/safety follow-up phase of the trial with ongoing SD, PR, or CR will continue to have tumor imaging completed every 12 weeks for the first year following the Clinical/Safety Follow-up period and then as per standard of care (minimum of every 6 months) until disease progression or withdrawal of consent
Survival Status					
Assessment Subject Survival Status				X	Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) for up to 3 years following the first dose of study drug. The nature and start dates of any new therapies during this period will be recorded.

[a] Follow-up visits at Days 30, 60 and 100 (±7 days) should occur after the last dose or coinciding with the date of discontinuation ±7 days if date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

Table 5.1-4: Retreatment Screening Procedural Outline (CA186107)		
Procedure	**Screening Visit (Day -28 to -1)**	**Notes**
Eligibility Assessments		
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 24 hours of dosing on Cycle 1Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Performance Status	X	ECOG Performance Status (Appendix 4).
Physical Measurements	X	Weight.
Vital Signs	X	Includes body temperature, seated blood pressure, heart rate and respiratory rate. Blood pressure, heart rate and respiratory rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation	X	Pulse oximetry collected at rest. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not used in isolation to document or diagnosis pulmonary toxicity.
Revised International Prognostic Index (IPI) and Follicular Lymphoma International Prognostic Index (FLIPI)	X	For subjects with B-cell NHL only. Refer to Appendix 5
Electrocardiogram (ECGs)	X	12-lead ECG; ECGs should be recorded after the subject has been supine for at least 5 minutes if not done within the last 6 months
Laboratory Tests		**Laboratory tests listed below must be completed within 2 weeks of Retreatment Day 1 unless otherwise noted**
Chemistry (Excluding LFTs)	X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, fasting glucose, total protein, albumin, amylase, lipase, CRP, ferritin, uric acid, and LDH.
CBC w/differential & platelets	X	
LFT assessments	X	AST, ALT, alkaline phosphatase, total bilirubin, and GGT

Table 5.1-4: Retreatment Screening Procedural Outline (CA186107)		
Procedure	**Screening Visit (Day -28 to -1)**	**Notes**
Urinalysis	X	Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
PT/PTT	X	
Serology Tests	X	Repeat the following if >6 months since last treatment: Hep B surface antigen, Hep C antibody, Hepatitis C viral load Note: Testing for HIV-1, HIV-2 must be performed at sites where mandated by local requirements
Thyroid Function Tests (TFT)	X	TSH with free T3 and free T4
Serum Pregnancy Test	X	WOCBP only.
Efficacy Assessments		
Diagnostic Imaging	X	CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X	Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases or who have not had brain imaging within 30 days of anticipated first study drug administration.
PET Scan	X	As clinically indicated for subjects with B-cell NHL
Bone Scan	X	As clinical indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Clinical Drug Supplies		
Subject Registration via IVRS	X	Ensure subject continues to meet eligibility for protocol treatment.

Table 5.1-5: Retreatment Procedural Outline (CA186107)

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Safety Assessments						
Physical Examination (PE)	X					A targeted (symptom directed) PE performed by the investigator or designee is required at each subsequent visit.
Performance Status	X	X	X	X		ECOG score prior to dosing (Appendix 4)
Physical Measurements	X	X	X	X		Weight only prior to dosing
Vital Signs	X	X	X	X		Vital signs (body temperature, seated blood pressure, heart rate and respiratory rate) will be obtained before the BMS-936558 infusion, after the BMS-936558 infusion, before the BMS-663513, and after the BMS-663513 infusion. Subjects must be observed for 30 minutes after the BMS-663513 infusion before discharge. If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated. 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 examination, report changes on the appropriate non-serious or serious adverse event page. See Section 4.5.9 for treatment of infusion reaction.
Non-Serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 100 days after discontinuation of dosing. SAEs should be approved in TAO within 5 business days of entry
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

Table 5.1-5: Retreatment Procedural Outline (CA186107)

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Chest Radiograph						As clinically indicated.
Oxygen Saturation Levels	X	X	X	X		Collected pulse oximetry at rest prior to dosing.
Laboratory Tests	X	X	X	X		**On study labs (including pregnancy testing) to be done on site/local. Within 72 hrs prior to dosing**
Chemistry (excluding LFTs)	X	X	X	X		For all visits includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, CRP, ferritin, and LDH.
CBC with differential & platelets	X	X	X	X		Should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7-1
LFT assessments	Weekly during treatment with urelumab and for 8 weeks following last urelumab dose then Days 1, D15, D29 and D43 of each subsequent cycle					Includes AST, ALT, total bilirubin, alkaline phosphatase and GGT. LFTs will be monitored weekly during treatment with urelumab and for 8 weeks following the last dose of urelumab
TFT	X					To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Urinalysis	X	X	X	X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy Serum or Urine Test for WOCBP	X	X	X	X		Urine or Serum within 24 hours prior to treatment, the minimum sensitivity of the pregnancy test must be 25 IU/L or equivalents of HCG. If pregnancy test is positive, subject must not receive study drug. Pregnancy test must be performed at a minimum of every 4 weeks in the event of dosing delays.

Table 5.1-5: Retreatment Procedural Outline (CA186107)

Procedure	Cycles 1-6					Notes
	D 1a (-2 days)	D 15 (± 2 days)	D 29 (± 2 days)	D 43 (± 2 days)	D 49-56	
Sample Collection						
Pharmacokinetic (PK) Assessments						See Table 5.5.1-3
Immunogenicity Assessments						See Table 5.5.1-3
Biomarker Assessments						See Table 5.7-3
Efficacy Assessments						
Diagnostic Imaging					X	By methods used at baseline. CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging					X	As clinically indicated
Bone Scan					X	As clinically indicated
PET Scan					X	Required to confirm a CR for subjects with B-cell NHL
Bone marrow aspirate and biopsy					X	Required to confirm CR in subjects with B-cell NHL with bone marrow disease at screening
Clinical Drug Supplies						
BMS-936558 Administration	X	X	X	X		
BMS-663513 Administration (Cohort 1, 2, C)	X		X			Cohort 1,2, C To start administration no sooner than 30 minutes after completion of the BMS-936558 infusion.

Abbreviations: D=Day

[a] Day 1 of each cycle except where noted

Table 5.1-6: Retreatment Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival /Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
Safety Assessments					
Physical Examination (PE)	X	X	X		
Vital Signs	X	X	X		Includes body temperature, seated blood pressure, heart rate and respiratory rate. Blood pressure, heart rate and respiratory rate should be measured after the subject has been seated quietly for at least 5 minutes.
Performance Status	X	X	X		ECOG score (Appendix 4)
[redacted]	[redacted]	[redacted]			
Monitor for non-Serious Adverse Events	X	X	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 100 days after discontinuation of dosing. SAEs should be approved in TAO within 5 business days of entry
Laboratory Tests					
Chemistry (excluding LFTs)	X	X	X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, CRP, ferritin, and LDH.

Table 5.1-6: Retreatment Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival /Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
CBC with differential & platelets	X	X	X		Should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7-1
LFT assessment	Weekly for 8 weeks following last urelumab (if applicable) and at 30 Day, 60 Day, 100 Day follow-up				LFTs will be monitored weekly for 8 weeks following the last dose of urelumab. Includes AST, ALT, total bilirubin, alkaline phosphatase and GGT
TFT	X	X	X		To include TSH with reflex testing (free T3 and free T4).
Urinalysis	X	X	X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy Serum or Urine Test For WOCBP	X	X	X		The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalents of HCG.
Sample Collection					
Pharmacokinetic (PK) Assessments	X	X	X		See Table 5.5.1-3
Immunogenicity (ADA) Assessments	X	X	X		See Table 5.5.1-3
Efficacy Assessments					
Diagnostic Imaging			X	X	By method used at baseline. CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.

Table 5.1-6: Retreatment Follow-up Procedural Outline (CA186107)

Procedure	Clinical/Safety Follow-up			Survival /Long-Term Follow-up	Notes
	1 30 days[a] (± 7 days)	2 60 days (± 7 days)	3 100 days (± 7 days)	every 12 weeks (± 2 weeks)	
					Subjects who discontinue the clinical/safety follow-up phase of the trial with ongoing SD, PR, or CR will continue to have tumor imaging completed every 12 weeks for the first year following the Clinical/Safety Follow-up period and then as per standard of care (minimum of every 6 months) until disease progression or withdrawal of consent
Survival Status					
Assessment Subject Survival Status				X	Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) for up to 3 years following the first dose of study drug. The nature and start dates of any new therapies during this period will be recorded.

[a] Follow-up visits at Days 30, 60 and 100 (±7 days) should occur after the last dose or coinciding with the date of discontinuation ±7 days if date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

5.1.1 Retesting During Screening Period

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

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

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, a pulse oximeter for measuring oxygen saturation, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support (ACLS) cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-70°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and investigator brochures for urelumab and nivolumab. Case report forms (electronic or hard copy) will be provided by BMS as well as a copy of NCI CTCAE v4.0.Instructions for local laboratory data entry will be provided. The Central Laboratory will provide labels and tubes for the collection of blood samples for PK/biomarker and for genotyping analysis and tissue samples.

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 100 days after the last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be graded according to the NCI CTCAE v4.0. Subjects should be followed until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator.

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 subject registration. The baseline physical examination should include weight, height, heart rate, blood pressure, temperature, and ECOG status and should be performed within 28 days of treatment arm assignment. [redacted].

Subjects will be considered evaluable for safety if they have received any dose of either study drug. Toxicity assessments will be continuous during the Treatment period and the Clinical/Safety Follow-up periods.

Body weight and performance status should be assessed at each on-study visit. Vital signs will be obtained before the nivolumab infusion, after the nivolumab infusion, before the urelumab infusion, and after the urelumab infusion. Subjects must be observed for 30 minutes after the urelumab infusion before discharge. If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated. The start and stop time of the study drug infusion should be documented. Any new or worsening clinically significant changes must be reported on the appropriate non-serious or serious adverse event page.

5.3.1 Hepatotoxicity Assessment

Hepatotoxicity will be monitored using weekly liver function tests (LFTs) including AST, ALT, alkaline phosphatase, total bilirubin, and GGT during the 6 cycles where subjects are receiving combined treatment with urelumab and nivolumab (Table 5.1-2), and also weekly for the first 8 weeks following the last dose with urelumab. Following this period of weekly assessments, LFTs will also be monitored at all 3 clinical/safety follow-up visits (Table 5.1-3). A management algorithm for the monitoring and management of hepatotoxicity is included in Appendix 3.

5.3.2 Imaging Assessment for the Study

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

5.3.3 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 or Day -2 must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology
CBC with differential and platelets

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Gamma-glutamyl transferase (GGT)
Creatinine
Blood Urea Nitrogen (BUN)
Glucose (Fasting at screen visit)
Ferritin
Amylase
Lipase
Total Protein
Albumin
Sodium
Potassium
Chloride
Carbon dioxide
Calcium
Phosphorus
C-reactive protein (CRP)
Magnesium
Uric Acid

Urinalysis
Protein
Glucose
Blood

Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Serology

Serum for hepatitis C antibody, hepatitis C viral load, hepatitis B surface antigen, Hepatitis A IgM, HIV-1, -2 antibody, HPV status (screening only); HIV-1, -2 antibody at sites where mandated at screening only

Other Analyses

Protime(PT)/Prothrombin Time (PTT)
Thyroid Function Tests: Free T4, Free T3 and TSH
Pregnancy test (WOCBP only: screening, during dosing at predose and at a minimum of every 4 weeks, as well as Day 30, 60 and 100 follow-up visits).

Clinical laboratories will be assessed (see Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6).

Sites should collect these samples between -28 to -1 days from registration to ensure that results required for eligibility purposes are verified prior to registration. Pregnancy testing must be performed at screening, within 24 hours prior to each administration of study drug and at a minimum of every 4 weeks in the event of dosing delays. In addition pregnancy testing should be performed at Day 30, 60 and 100 follow-up visits. CBC plus differential and serum chemistry panel should be drawn within 72 hours prior to each subsequent scheduled cycle. On-study laboratory tests will be performed on site/locally. Laboratory tests may be obtained more frequently if indicated. Additional laboratory tests should be performed as per standard of care.

Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the Clinical/Safety Follow-up period via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

5.4 Efficacy Assessments

Disease assessment with computed tomography (CT) and/or magnetic resonance imaging (MRI) as appropriate will be performed at baseline and every 8 weeks until confirmed disease progression, at the completion of follow-up, or until subjects withdraw from the study. For subjects with B-cell NHL positron emission tomography (PET) will be performed at baseline and in order to confirm a complete response. Disease assessments at other timepoints may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator for appropriate populations of subjects as defined by RECIST v1.1[74] (see Appendix 1) for subjects with solid tumors and IWG (see Appendix 2) for subjects with B-cell NHL. For subjects with marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm a CR. At the sponsor's discretion, scans and measurements may be collected centrally to be reviewed by independent radiologists using IWG, RECIST v1.1, or other criteria at a later date, or at any time during the study.

Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST or IWG criteria. Investigators will also report the number and size of new lesions that appear while on-study. The timepoint tumor assessments will be reported on the CRF based on investigators' assessment using RECIST or IWG criteria. Please refer to Appendix 1 for specifics of RECIST v1.1 and Appendix 2 for specifics of the IWG criteria to be utilized in this study.

[redacted]

s.

[redacted]

Table 5.5.1-1: Pharmacokinetic Sampling Schedule (Dose Escalation)

Study Day	Event	Time (relative to Nivolumab dosing)	Urelumab		Nivolumab	
			PK Sample	ADA Sample	PK Sample	ADA Sample
C1D1	0 h (pre-dose)[a]	00:00		X		X
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
	4 h	04:00	X		X	
	6 h	06:00	X		X	
C1D8	168 h	168:00	X		X	
C1D15	0 h (pre-dose)	00:00	X		X	
C1D29	0 h (pre-dose)	00:00	X	X	X	X
C1D36	168 h	168:00	X		X	
C1D43	0 h (pre-dose)	00:00	X		X	
C2D1	0 h (pre-dose)	00:00	X	X	X	X
C2D29	0 h (pre-dose)	00:00	X		X	
C3D1	0 h (pre-dose)	00:00	X	X	X	X
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C3D8	168 h	168:00	X		X	
C3D15	0 h (pre-dose)	00:00	X		X	
C3D29	0 h (pre-dose)	00:00	X	X	X	X
C3D36	168 h	168:00	X		X	
C3D43	0 h (pre-dose)	00:00	X		X	
C4D1	0 h (pre-dose)	00:00	X	X	X	X
C5D1	0 h (pre-dose)	00:00	X	X	X	X
C6D1	0 h (pre-dose)	00:00	X	X	X	X
30 Day Follow-Up			X	X	X	X
60 Day Follow-Up[c]			X	X	X	X

Table 5.5.1-1: Pharmacokinetic Sampling Schedule (Dose Escalation)

Study Day	Event	Time (relative to Nivolumab dosing)	Urelumab		Nivolumab	
			PK Sample	ADA Sample	PK Sample	ADA Sample
100 Day Follow-Up[c]			X	X	X	X

[a] All subsequent urelumab predose samples can be collected at same time as the nivolumab predose sample

[b] 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). If the end of infusion is delayed to beyond the normal infusion duration of 1 hour, the collection of this sample should be delayed accordingly. Urelumab predose samples can be collected at same time as the nivolumab predose sample.

[c] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 5.5.1-2: Pharmacokinetic Sampling Schedule (First 6 Subjects in Stage 1 Expansion)

Study Day	Event	Time (relative to Nivolumab dosing)	Urelumab		Nivolumab	
			PK Sample	ADA Sample	PK Sample	ADA Sample
C1D1	0 h (pre-dose)[a]	00:00	X	X	X	X
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
	4 h	04:00	X		X	
	6 h	06:00	X		X	
C1D8	168 h	168:00	X		X	
C1D15	0 h (pre-dose)	00:00	X		X	
C1D29	0 h (pre-dose)	00:00	X	X	X	X
C2D1	0 h (pre-dose)	00:00	X	X	X	X
C3D1	0 h (pre-dose)	00:00	X		X	
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C3D8	168 h	168:00	X			
C3D15	0 h (pre-dose)	00:00	X			
C3D29	0 h (pre-dose)	00:00	X			
C4D1	0 h (pre-dose)	00:00	X	X	X	X
C6D1	0 h (pre-dose)	00:00	X	X	X	X
60 Day Follow-Up[c]			X	X	X	X
100 Day Follow-Up[c]			X	X	X	X

[a] All subsequent urelumab predose samples can be collected at same time as the nivolumab predose sample

[b] 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). If the end of infusion is delayed to beyond the normal infusion duration of 1 hour, the collection of this sample should be delayed accordingly. Urelumab predose samples can be collected at same time as the nivolumab predose sample.

[c] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 5.5.1-3: Pharmacokinetic Sampling Schedule (After 6 subject in Stage 1 Expansion, all subjects in Stage 2 Expansion and Retreatment)

Study Day	Event	Time (relative to Nivolumab dosing)	Urelumab		Nivolumab	
			PK Sample	ADA Sample	PK Sample	ADA Sample
C1D1	0 h (pre-dose)[a]	00:00	X	X	X	X
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C1D29	0 h (pre-dose)	00:00	X	X	X	X
C2D1	0 h (pre-dose)	00:00	X	X	X	X
C3D1	0 h (pre-dose)	00:00	X		X	
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C4D1	0 h (pre-dose)	00:00	X	X	X	X
C6D1	0 h (pre-dose)	00:00	X	X	X	X
60 Day Follow-Up[c]			X	X	X	X
100 Day Follow-Up[c]			X	X	X	X

[a] All subsequent urelumab predose samples can be collected at same time as the nivolumab predose sample.

[b] 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). If the end of infusion is delayed to beyond the normal infusion duration of 1 hour, the collection of this sample should be delayed accordingly. Urelumab predose samples can be collected at same time as the nivolumab predose sample.

[c] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 5.5.1-4: Pharmacokinetic Sampling Schedule (Subjects with Melanoma PD-L1 negative)

Study Day	Event	Time (relative to Nivolumab dosing)	Urelumab		Nivolumab	
			PK Sample	ADA Sample	PK Sample	ADA Sample
C1D1	0 h (pre-dose)[a]	00:00	X	X	X	X
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C1D29	0 h (pre-dose)	00:00	X	X	X	X
C2D1	0 h (pre-dose)	00:00	X	X	X	X
C3D1	0 h (pre-dose)	00:00	X		X	
	1 h (EOI nivolumab)[b]	01:00			X	
	2 h (EOI urelumab)[b]	02:00	X			
C4D1	0 h (pre-dose)	00:00	X	X	X	X
C6D1	0 h (pre-dose)	00:00	X	X	X	X
60 Day Follow-Up[c]			X	X	X	X
100 Day Follow-Up[c]			X	X	X	X

[a] All subsequent urelumab predose samples can be collected at same time as the nivolumab predose sample.

[b] 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). If the end of infusion is delayed to beyond the normal infusion duration of 1 hour, the collection of this sample should be delayed accordingly. Urelumab predose samples can be collected at same time as the nivolumab predose sample.

[c] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

[redacted]

[redacted]

[redacted]

[redacted]

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization). Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI).

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than remedying ill health state and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)
- admission for administration of anticancer therapy in the absence of any other SAEs.

6.1.1 Serious Adverse Event Collection and Reporting

The Investigator Brochures (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 (eg, a follow-up skin biopsy).

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

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

SAE Telephone Contact (required for SAE and pregnancy reporting): See 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 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 that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

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

6.3 Laboratory Test Result Abnormalities

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

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

It is expected that wherever possible, the clinical, rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

The investigator must immediately notify the BMS Medical Monitor (or designee) 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) Aminotransferase (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

6.7 Other Safety Considerations

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

6.7.1 Treatment Algorithms for Drug-related Adverse Events

Treatment algorithms for the management of potential drug-related adverse events are located in Appendix 3.

6.7.2 Rapid Notification of Other Adverse Events of Interest

In addition to serious adverse events, overdose, and pregnancy, the following adverse events will also be reported on an expedited basis to the BMS Medical Monitor or Study Director by phone or e-mail:

- Adverse events that potentially meet DLT criteria; see section 4.5.2
- Any potential Hy's Law case (> 3 x ULN of either ALT/AST with concurrent > 2 x ULN of Total Bilirubin and no alternate etiology)
- ≥ Grade 2 study-drug related adverse events (including neurologic toxicity)
- ≥ Grade 2 diarrhea/colitis
- ≥ Grade 3 motor neurologic toxicity regardless of causality

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation

In dose escalation, the sample size at each dose cannot be determined exactly, as it depends on the number of observed toxicities. Between 3 and 12 subjects approximately are expected to be treated during dose escalation in each dose level.

8.1.2 Cohort Expansion

8.1.2.1 Stage 1

During Stage 1 of cohort expansion, approximately 20 subjects in each tumor type will be treated at the MTD/HAD dose level and schedule. A sample size of approximately 20 subjects in each tumor type in Stage 1 is intended to provide a better picture of the safety of each regimen. For example, if a low grade adverse event were observed in 3 or fewer patients, the 90% 1-sided upper confidence interval would be 30%. In addition, it allows for a futility assessment. In general, if the true response rate is 20%, 30%, 40%, or 50%, the probability of seeing 4 or more responses in the 20 patients is 58.9%, 89.3%, 98.4%, and 99.9%, respectively. If the true response rate is 30%, the likelihood of seeing less than 4/20 responses is 10.7% (false negative rate). Conversely, if the true response rate is 10%, the likelihood of seeing 4or more responses is 13.3% (false positive rate).

8.1.2.2 Stage 2:

During Stage 2 of cohort expansion, up to approximately 20 additional subjects will be treated in each tumor type. This will allow for further establishment of the safety profile of the combination and a preliminary assessment of efficacy. The total of approximately 40 subjects (20 from Stage 1 Expansion and 20 from Stage 2) is designed to provide higher precision around estimates of safety and preliminary efficacy. If in a cohort of 40 subjects 7, 10, or 15 responses are observed, then the

lower limit of the one-sided 90% exact binomial CI for the ORR is 10%, 16%, and 27% respectively. These calculations are made using the Clopper-Pearson method for exact confidence intervals. If the true ORR in a tumor type is 50%, then with 40 subjects in a tumor type, there is 96% chance of observing at least 15 responses, and 87% chance of observing at least 17 responses, and there is 8% chance of observing 15 or fewer responses (false negative rate).

An additional 50 treatment naïve PD-L1 negative melanoma subjects will be treated at MTD/HAD to further evaluate if there is an efficacy signal in this population. Additional subjects may be enrolled and treated so as to accrue a minimum of 50 evaluable subjects with at least 2 on treatment scans. These 50 PD-L1 negative melanoma patients will be combined for analysis with approximately 18 PD-L1 negative melanoma patients from Cohort 2 for a total of 68 PD-L1 negative melanoma patients. Assuming an ORR of approximately 56%, a minimum of 38/68 responders would provide a 95% Clopper-Pearson confidence interval with a lower limit above 42%.

8.2 Populations for Analyses

- All Enrolled Data set: subjects who signed informed consent and registered in the study.
- All Treated Data set: all subjects who received at least one dose of either study drug.
- Response-Evaluable Data Set: all treated subjects who receive either study drug, have a baseline tumor assessment with measurable disease, and one of the following:
  - at least one evaluable on-treatment tumor assessment prior to subsequent therapy,
  - clinical progression prior to subsequent therapy, or
  - death, if death occurs within 100 days after last dose.
- Urelumab Pharmacokinetic Data Set: all subjects who receive at least one dose of urelumab and have adequate serum concentration data for urelumab PK.
- Nivolumab Pharmacokinetic Data Set: all subjects who receive at least one dose of nivolumab and have adequate serum concentration data for nivolumab PK.
- Urelumab Immunogenicity Data Set: all subjects who receive at least one dose of urelumab with baseline and at least one post-baseline urelumab ADA assessment available.
- Nivolumab Immunogenicity Data Set: all subjects who receive at least one dose of nivolumab with baseline and at least one post-baseline nivolumab ADA assessment available.
- Biomarker Data Set: all treated subjects who have evaluable biomarker data available.

8.3 Endpoint Definitions

Safety is the primary endpoint in this Phase 1/2 study. All subjects who receive at least one dose of urelumab or nivolumab will be evaluated for safety as measured by the occurrence of adverse events, serious adverse events, deaths and laboratory abnormalities, assessed during treatment and for 100 days in follow-up.

8.3.1 Primary Endpoint(s)

The primary objective (to assess the safety and tolerability of urelumab given in combination with nivolumab and to identify dose limiting toxicities (DLTs) and the maximally tolerated dose (MTD) of the combination) will be measured by the following primary endpoints.

a) Incidence of adverse events: all non-serious adverse events will be collected from Day 1 until 100 days after the subject's last dose of study drug or until they discontinue the study as per Section 3.5. All serious adverse events must be collected from the date of the subject's written consent until 100 days after discontinuation of dosing or until they discontinue the study as per Section 3.5.
b) Incidence of clinical laboratory test abnormalities including hematology and serum chemistry, and thyroid panel abnormalities, assessed at specified time points as designated in the Time and Events Section (5.1).

Assessments will be based on adverse event reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, imaging studies, and clinical laboratory tests. Adverse events will be categorized using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA); both AEs and laboratory tests will be graded using NCI CTCAE v4.0. All subjects who receive study drug therapy will be evaluated for safety as measured by the rate of adverse events (AEs), and serious adverse events (SAEs), and will be assessed during treatment and for 100 days in follow-up.

8.3.2 Secondary Endpoints

8.3.2.1 Efficacy Endpoints

The secondary objective of assessing preliminary anti-tumor activity will be based on endpoints described below using RECIST v1.1 and investigator assessed response per IWG criteria for lymphomas.

Best overall response (BOR) is the best response designation recorded between the start of the study treatment and the date of objectively documented progression based on RECIST v1.1 (or relapsed based on IWG) taking into account any requirement for confirmation, or the date of subsequent anti-cancer therapy, whichever occurs first in the study. CR or PR determinations included in the BOR assessment must be confirmed by a consecutive second (confirmatory) evaluation meeting the criteria for response that is performed at least 4 weeks after the criteria for response are first met. **When SD is believed to be the best response, it must meet a minimum SD duration of 49 days. Measurements must have met the SD criteria at least once after study entry.** The above will be determined based on tumor measurements occurring every 8 weeks during the Treatment period (Cycle 1 Day 1 through Cycle 6 Day 56), and at planned timepoints during the Clinical/Safety Follow-up period.

Study level endpoints used to assess this objective are defined as follows:

Objective response rate (ORR) is defined as the total number of subjects whose BOR is either CR or PR divided by the total number of subjects in the population of interest.

Duration of Response (DOR) computed only for subjects with a BOR of CR or PR is defined as the number of days between the date of first response and the subsequent date of objectively documented disease progression based on the criteria (RECIST v1.1) or relapse based on IWG, or death due to any cause, if death occurred within 100 days after last dose, whichever occurs first. If death is more than 100 days after last dose, then DOR is censored at the last tumor assessment date. 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. Subjects who receive subsequent therapy will be censored at the start of subsequent therapy.

Progression-Free Survival Rate (PFSR) is defined as the probability of a subject remaining progression-free and surviving a specific length of time (eg, 24 weeks). The PFS for a given subject will be computed based on the number of days between the first dose of study drug and progressive disease, relapse, or death due to any cause, if death occurred within 100 days after last dose. The PFSR will be estimated using Kaplan-Meier methods. For those subjects who remain alive and have not progressed, PFS will be censored on the date of the last tumor assessment. Subjects who did not have any on study tumor assessment and did not die will be censored on the date of first dose of study medication. The above will be calculated based on tumor measurements occurring every 8 weeks during treatment and at planned timepoints during the Clinical/Safety Follow-up period.

8.3.2.2 Pharmacokinetics (PK)

Urelumab and nivolumab maximum concentration (Cmax [µg/mL]), end of infusion concentration (Ceoinf), time to maximum concentration (Tmax [hr]), trough concentration (Ctrough [µg/mL]), area under the curve (AUC[0-T] and AUC[TAU] [µg.hr/mL]) will be evaluated using non-compartmental analysis in all study subjects. (Table 5.5.1-1)

8.3.2.3 Immunogenicity

Occurrence of specific anti-drug antibodies to urelumab and nivolumab will be determined from measurements obtained at planned timepoints specified in Table 5.5.1-1).

Endpoints for the study are incidence rates of persistent positive ADA as well as neutralizing positive ADA from initiation of each drug treatment up to and including the follow-up period of the last study drug dosed. Based on recommendation from BMS Immunogenicity Council, Harmonization of Clinical Immunogenicity Reporting by an Initiative of the Therapeutic Protein Immunogenicity Focus Group of the American Association Pharmaceutical Scientists, and the FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products, the following definitions will be applied:

ADA Status of a Subject:

- Baseline ADA Positive Subject: A subject with baseline ADA positive sample
- ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment during the defined observation time period.
- ADA Negative Subject: A subject with no ADA positive sample after the initiation of treatment

Definitions for potential ADA Status of a Sample (Baseline ADA Positive, ADA Positive, or ADA Negative), as well as sub-categories of ADA Positive Subject such as Persistent Positive, Only the Last Sample Positive, Other Positive and Neutralizing Positive will be provided in the statistical analysis plan (SAP).

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, and height will be collected, and Body Mass Index (BMI) will be derived.

8.4.2 Efficacy Analyses

Individual best overall response (BOR), duration of response and PFS will be listed using RECIST v1.1 and IWG criteria, as appropriate. BOR outcomes will be tabulated by disease type and treatment (eg, with a column for each dose/regimen combination). The objective response rate (ORR) and PFS rate (eg, at 24 weeks) and corresponding confidence interval will be provided by tumor type and treatment. The duration of response and PFS will be estimated by Kaplan-Meier (K-M) methodology by disease type, depending on data availability. PFS rates at 24 weeks will be similarly estimated, based on K-M methodology. ORR, duration of response and PFS analyses will include subjects in the cohort expansion phase and subjects in dose escalation matching those in cohort expansion by disease type and treatment. Individual changes in the tumor burden over time may be presented graphically within a disease type. Landmark overall survival will be assessed as part of exploratory efficacy analysis, using Kaplan-Meier plots and the median (as measured using Kaplan-Meier Method) for each tumor type.

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, tumor type, and treatment arm. Vital signs and clinical laboratory test results will be listed and summarized by tumor type and treatment arm. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for the pharmacokinetic parameters by tumor type, dose, regimen, study day and time on urelumab PK subjects and nivolumab PK subjects, where data is available. This data may also be pooled with other datasets for population PK analysis which will be part of a separate report.

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses

Not applicable.

8.4.7 Other Analyses

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive anti-drug antibody (ADA) at any time point will be provided by treatment for each analyte. Finally, the number (%) of subjects with the following anti-drug responses will be reported for each analyte if applicable, by dose, and overall: Baseline ADA Positive, ADA Positive (Persistent Positive, Only the Last Sample Positive), ADA Positive with Neutralizing Positive, and ADA Negative

To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be summarized by overall immunogenicity status. Associations between trough concentrations of urelumab (or nivolumab) and corresponding ADA assessments may also be explored.

8.5 Interim Analyses

Data emerging from this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final lock of the study database. Additional interim analyses may also be performed for administrative purposes or publications. Analyses will only consist of listings, summaries, and graphs of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use response evaluable or all treated populations depending on the purpose of the analysis.

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 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 to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study 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 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 a qualified physician who is an investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory Investigator will be selected considering the following criteria.

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. Expanded definition Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
Medical Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of Medical Research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.
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

Term	Definition
	events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
ADA	anti-drug antibodies
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
ALK	anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
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
β-HCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BRAF	B-Rapidly Accelerated Fibrosarcoma
BTLA	B- and T-Lymphocyte Attenuator

Term	Definition
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
$C1^{-}$	chloride
CLcr	creatinine clearance
CLT	total body clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CR	complete remission (IWG criteria) or complete response (RECIST)
CRC	Colorectal Cancer
Crcl	creatinine clearance
CRF	Case Report Form, paper or electronic
CRP	c-reactive protein
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTLA4	Cytotoxic T Lymphocyte Antigen 4
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough observed plasma concentration
dL	deciliter
DLBCL	diffuse large B cell lymphoma
DNA	deoxyribonucleic acid
DLT(s)	Dose Limiting Toxicity(ies)
DOR	Duration of Response
ECG	electrocardiogram

Term	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
eg	exempli gratia (for example)
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FPE	formalin-fixed paraffin-embedded
FNA	fine needle aspiration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
GnRH	gonadotropin releasing hormone
HAD	highest administered dose
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HCC	hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
HSCT	Hematopoietic stem cell transplant
ICD	International Classification of Diseases
ICOS	Inducible T-cell Co-stimulator

Term	Definition
ie	id est (that is)
IEC	Independent Ethics Committee
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IWG	International Working Group
K^+	potassium
kg	kilogram
KIR	Killer-cell Immunoglobulin-like Receptors
K-M	Kaplan-Meier
L	liter
LCM	laser capture microdissection
LDH	lactate dehydrogenase
LFT	Liver Function Test
MDSCs	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
µg	microgram
Na^+	sodium
N/A	not applicable
NCI	National Cancer Institute
ng	nanogram

Term	Definition
NHL	non-Hodgkin's lymphoma
NK	natural killer
NSCLC	non small cell lung cancer
NSAID	nonsteroidal anti-inflammatory drug
ORR	Overall Response Rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1
PE	physical exam
PET	positron-emission tomography
PFS	progression free survival
PFSR	progression-free survival rate
PK	pharmacokinetics
PR	partial remission (IWG) or partial response (RECIST)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of head and neck
SD	standard deviation or stable disease (RECIST)
SHP-1, -2	Src homology region 2 domain-containing phosphatase-1, -2
SNP	single nucleotide polymorphism
SOP	standard operating procedures
TAO	Trial Access Online, the BMS implementation of an EDC capability

Term	Definition
Tbili	Total bilirubin
T-HALF (t1/2)	Half life
TIA	transient ischemic attack
TIL(s)	tumor infiltrating lymphocyte(s)
Tmax, TMAX	time of maximum observed concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Vss/F (or Vss)	apparent volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential