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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

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**STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT**

**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**

PROTOCOL(S) CA186107

VERSION # 1.3

Table 1: Document History

Version Number	Author(s)	Description
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2 STUDY DESCRIPTION

2.1 Study Design

Main points of the study design are described below. For more details, see Protocol Section 3.1¹. 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-Hodgkins Lymphoma (NHL). The second phase of the study will include a 2-stage cohort expansion in multiple tumors types (melanoma [MEL], non-small cell lung cancer [NSCLC], head and neck squamous cell carcinoma [SCCHN], diffuse large B cell lymphoma [DLBCL]), and follicular lymphoma (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 the Protocol Section 3.3¹. Study periods are described in [Section 6.1](#).

2.1.1 Dose Escalation

Table 2: 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.

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 2](#). 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).

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. 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 will be followed.

Table 3: Decision Rules During Dose Escalation

Number of Evaluable Subjects/ Cohort	3-4 ^c			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 in cohort to reach at least 9 subjects	Dose exceeds MTD	Dose Escalate	Dose exceeds MTD

^c 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 4).

Table 4: 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	8 mg IV every 8 weeks	1 mg/kg or 80 mg IV every 2 weeks
C ^b	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 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 4](#) 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.

2.1.2 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 be conducted in 2 parts as outlined below in Table 5.

Table 5: Cohort Expansion

Tumor Types	Stage 1 Expansion	Stage 2 Expansion
Non-small Cell Lung Cancer (NSCLC-NAIVE)	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) (NSCLC-PROG)	Up to approximately 20 subjects at MTD or HAD	Up to approximately 20 subjects

Table 5: 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

2.1.2.1 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 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).

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.

2.1.2.2 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.

2.2 Treatment Assignment

After the subject's eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling into an interactive voice response system (IVRS) to obtain the subject number. The study treatments include BMS-663513 (urelumab) and BMS-936558 (nivolumab). Subjects will be treated at dose levels as specified in [Table 2](#) and [Table 4](#).

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This statistical analysis plan (SAP) incorporates the global protocol amendments listed in Table 6.

Table 6: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Amendment 01	09-Jul-2014	Inclusion of pharmacogenetic data collection and statistical analysis
Amendment 02	06-Mar-2015	Updates to the inclusion/exclusion criteria, re-treatment phase, and PK sampling and biomarker assessments.
Amendment 03	29-Jun-2015	Changed Nivolumab dosing from mg/kg to mg flat dosing, updated the duration of therapy for both drugs, updates made to the PK endpoints and analyses.
Amendment 04	30-Aug-2015	Removed randomization and Q8W dosing arms from cohort expansion.
Amendment 05	22-Dec-2015	Added 2 tumor types (NSCLC-PROG and FL).

3 OBJECTIVES

3.1 Primary

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

3.2 Secondary

- 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 PK of urelumab and nivolumab when co-administered.
- To monitor immunogenicity of urelumab and nivolumab administered as combination therapy.

[REDACTED]

[REDACTED]

[REDACTED]

- To assess the overall survival (OS) following the start of therapy with the combination of urelumab and nivolumab.

4 ENDPOINTS

4.1 Primary Endpoint

All subjects who receive at least one (full or partial) dose of urelumab or nivolumab will be evaluated for safety as measured by the occurrence of adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory abnormalities. All non-serious AEs will be assessed from the start of dosing. All SAEs and deaths will be assessed from the date of the subject's written informed consent. All AEs (serious and non-serious), and deaths will be assessed up to 100 days after the subject's last dose of study drug or until they discontinue the study as per Protocol Section 3.5¹. Incidence of clinical laboratory abnormalities will be assessed at specified timepoints described in Protocol Section 5.1.

In addition, the occurrence of abnormalities in vital signs, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests will be examined.

Adverse events will be categorized using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each database lock; both AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

4.2 Secondary Endpoints

4.2.1 Preliminary Antitumor Activity

Tumor assessments will be performed every 8 weeks (\pm 1 week) during the treatment period (Cycle 1 Day 1 through Cycle 6 Day 56), and at planned timepoints during the clinical follow-up period. In addition, subjects who discontinue study drug for reasons other than progression will continue to have tumor assessments completed every 12 weeks for the first year and then continue to receive scans per standard of care guidelines for follow-up or at a minimum of every 6 months until disease progression or withdrawal of consent.

Changes in tumor measurements and tumor response will be assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1² for subjects with solid tumors and using the revised International Working Group (IWG) Criteria³ for subjects with B-cell NHL and Follicular Lymphoma. Investigators will also report the number and size of new lesions that appear while on-study. Endpoints will be defined based on all available tumor assessments.

The following set of efficacy study-level endpoints will be used.

- **Objective Response Rate (ORR):** The total number of subjects whose best overall response (BOR) is either a complete response or partial response for solid tumors and complete remission or partial remission for B-cell NHL, divided by the total number of subjects in the population of interest. Hereafter, complete response for solid tumors and complete remission

for B-cell NHL will both be referred to as complete response (CR); partial response for solid tumors and partial remission for B-cell NHL will both be referred to as partial response (PR).

- Best Overall Response: The subject's best response designation over the study as a whole, recorded between the date of first study drug administration and the date of objectively documented progression or relapse per RECIST 1.1 or IWG, with subsequent confirmation, or date of subsequent anti-cancer therapy, whichever occurs first in the study.
 - ◆ A minority of subjects may continue treatment beyond confirmed progression or relapse, as described in Protocol Section 3.5.1¹. For these subjects, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1 defined progression or IWG defined relapse or progressive disease.
 - ◆ Complete or partial responses in solid tumors may be claimed only if changes in tumor measurements are confirmed by a consecutive assessment meeting the criteria for response or remission and performed no less than 4 weeks (28 days) after the criteria for response were first met.
 - ◆ When stable disease (SD) is believed to be the best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry. The minimum criteria for SD duration (8 weeks) must have been satisfied (considering the ± 1 week tumor assessment window, 49 days will be used to derive SD).
- **Median Duration of Overall Response (mDOR):** The significance of ORR is assessed by its magnitude and duration of response. DOR is computed only for subjects with objectively defined CR or PR, and is defined as the time from first response to the subsequent date of objectively documented disease progression based on the criteria (RECIST 1.1) 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 duration of response is censored at the last tumor assessment date. Subjects who remain alive and have not progressed nor received subsequent therapy, will have their DOR censored on the date of their last tumor assessment. Subjects who receive subsequent therapy will be censored at the start of subsequent therapy.
- **Progression Free Survival Rate (PFSR) at Week X:** The proportion of subjects remaining progression free and surviving at X weeks, where X is a specific length of time, eg, 24 weeks, which will be determined by the data for each interim or final analysis and will be documented in the data presentation plan (DPP). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.
 - Progression Free Survival (PFS): The PFS for a subject is defined as the time from the date of first dose of study drug to the date of the first documented disease progression or relapse, or death due to any cause, if death occurred within 100 days after last dose. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Subjects who die within 100 days after last dose without a reported prior progression will be considered to have progressed on the date of their death. Subjects who remain alive and have not progressed 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 within 100 days after last dose of study medication will be censored on the date of first dose of study medication.

4.2.2 Pharmacokinetic Endpoints

The following PK parameters of urelumab derived from serum concentration time profile of subjects using non-compartmental analysis may be included for urelumab PK analysis, depending on the availability of data.

- C_{max} (µg/mL) (maximum concentration)
- T_{max} (hr) (time to maximum concentration)
- AUC(0-T) (µg.hr/mL) (area under the plasma concentration-time curve, 0 to time of last quantifiable concentration)
- AUC(TAU) (µg.hr/mL) (area under the concentration-time curve in one dosing interval, 0 to 28 days)
- C_{trough} (trough concentration)
- C_{eof} (end of infusion concentration)

In addition, the following PK parameters of nivolumab will be calculated at specified visits.

- C_{eof} (end of infusion concentration)
- C_{trough} (trough concentration)
- AUC(0-T) (µg.hr/mL)
- AUC(TAU) (µg.hr/mL) (area under the concentration-time curve in one dosing interval, 0 to 14 days)
- C_{max} (µg/mL)
- T_{max} (hr)

4.2.3 Immunogenicity

Immunogenicity of urelumab and nivolumab are measured by the detection of human antibodies against urelumab and nivolumab, respectively. Endpoints for the study are incidence rates of persistent positive Human Anti-Drug Antibody (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 and White Paper on Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations by Shankar et al⁴, and the Food and Drug Administration (FDA) Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products⁵, the following definitions will be applied for urelumab and nivolumab separately:

4.2.3.1 ADA Status of a Sample

- **Baseline ADA-Positive Sample:** ADA is detected in the last sample before initiation of treatment

- #### 4.2.3.2 *ADA Status of a Subject*

-

[illegible]

5 SAMPLE SIZE AND POWER

5.1 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.

5.2 Cohort Expansion

5.2.1 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 4 or more responses is 13.3% (False Positive Rate).

5.2.2 Stage 2

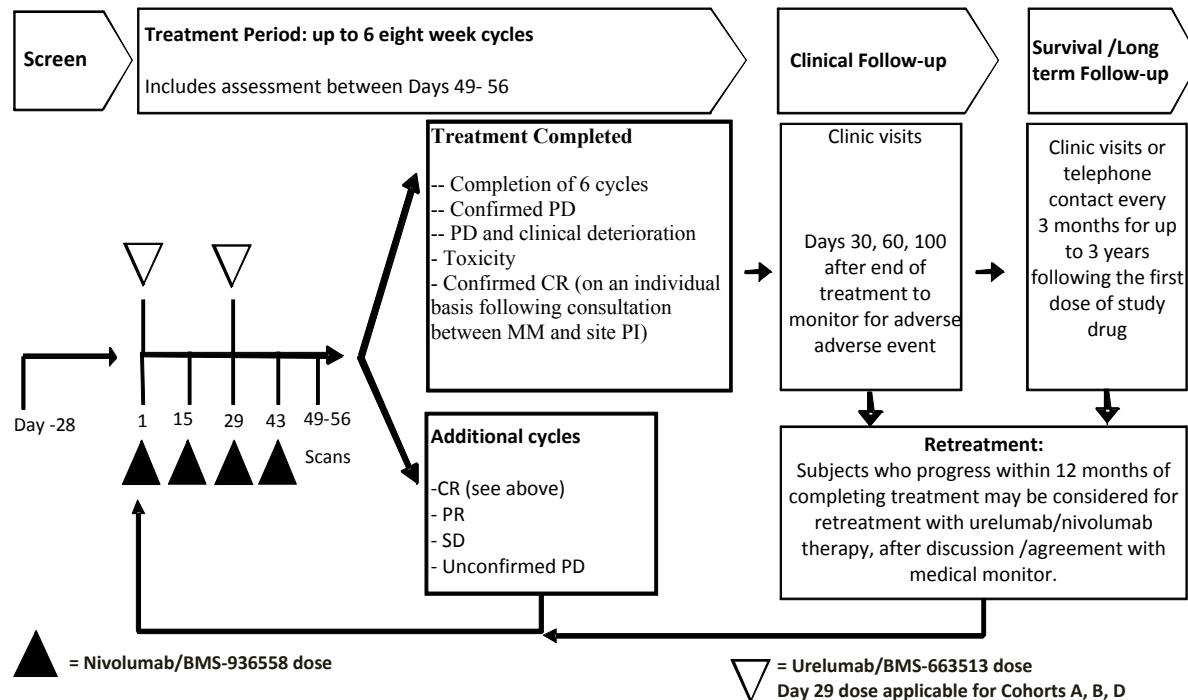
During Stage 2 of cohort expansion, up to approximately 20 additional subjects will be treated in each tumor type. This will allow for further establishment of the safety profile of the combination and a preliminary assessment of efficacy. The total of approximately 40 subjects (20 from Stage 1 Expansion 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 intervals⁶. 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).

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Subjects will complete up to four periods of the study (Screening, Treatment, Clinical/Safety Follow-up, and Survival/Long-term Follow-up). The total time on study for any individual subject is expected to be approximately 3.1 years. A study schematic is presented in [Figure 1](#).

Figure 1: Study Schematic



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

6.1.1 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).

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of either study drug. In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to, but not including, the date of the first dose of either study drug.
- Baseline evaluations (laboratory tests, pulse oximetry, and vital signs) will be defined as evaluations with a date on or prior to the date of first dose of either study drug, unless otherwise specified, since these procedures are to be performed prior to dosing as specified in Protocol Section 5.3 and Table 5.1-2¹.

If there are multiple valid assessments at baseline, then the assessment that is closest to the date (and time, if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time, if collected), then the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

6.1.2 Treatment Period

- Begins when the subject is assigned to a treatment arm
- Consists of up to 6 eight-week treatment cycles (48 weeks)
 - Nivolumab will be given every 2 weeks
 - Urelumab will be given every 4 weeks
 - On days where both study drugs are given, nivolumab will be given first followed by urelumab within 30 minutes of completing the infusion of nivolumab
 - Subjects may continue additional cycles of study therapy, up to a maximum of 6 cycles, on a case-by-case basis
- This period ends when the subject is discontinued from study therapy

6.1.3 Clinical Follow-up Period

- Begins from the date the decision was made to discontinue treatment (off treatment date)
- Subjects must be followed for at least 100 days after the last dose
- Follow-up visits should occur at Days 30, 60, and 100 (± 7 days) after the last dose or date of discontinuation

6.1.4 Survival/Long-term Period

- Study subjects will be followed every 3 months 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 every 12 weeks for the first year after discontinuation of study drug, and then continue to receive scans 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

6.1.5 Re-treatment with Study Therapy

The consideration to re-initiate study therapy under certain 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. Re-treatment may occur after subjects who complete all 6 cycles of treatment and within 12 months of last treatment. More details are discussed in the Protocol Section 4.5.8¹.

Subjects entering this phase will receive the study therapy at the same dose levels as assigned at study start and follow the time and events schedule described in the Protocol Tables 5.1-4 to 5.1-6¹.

All primary efficacy and safety analyses and exposure calculations for the CSR will exclude the re-treatment period, unless otherwise stated. Endpoints which use the date of last study drug as a cut-off refer to the last date of the original treatment period. The SAP and/or DPP may be amended for additional analyses if a substantial number of subjects enter the re-treatment period.

6.2 Treatment Regimens

Refer to [Table 2](#) and [Table 4](#) for treatment arms explored in this trial. Some of these arms might not have any subjects.

Certain analyses (eg, PFS and DOR) may include subjects in the dose escalation phase and subjects in the cohort expansion phase matched by disease type and regimen.

The treatment group “as assigned” will be retrieved from the IVRS system, if applicable. The treatment group “as treated” will be the drug combination that the subject actually received during the study, even if it is not the same as the arm that was assigned by IVRS. Unless otherwise specified, the safety analysis will be based on “as treated”.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an ICF and are registered into IVRS will be included. Subject disposition will be tabulated using this dataset.
- All Treated Subjects: All subjects who receive at least one dose of either study drug. This population will be used for safety and efficacy analyses unless otherwise specified.
- Response Evaluable Subjects: 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
 - Death, if death occurred within 100 days after last dose
- Urelumab PK Subjects: All subjects who receive at least one dose of urelumab and have adequate serum concentration data for urelumab PK.
- Nivolumab PK Subjects: All subjects who receive at least one dose of nivolumab and have adequate serum concentration data for nivolumab PK.
- Urelumab ADA Evaluable Subjects: All subjects who receive at least one dose of urelumab with baseline and at least 1 post-baseline urelumab immunogenicity assessment.
- Nivolumab ADA Evaluable Subjects: All subjects who receive at least one dose of nivolumab with baseline and at least 1 post-baseline nivolumab immunogenicity assessment.
- Biomarker Evaluable Subjects: All Treated Subjects with at least one evaluable measurement for a specific marker will be included in the dataset for that marker. Evaluable may differ depending on the analysis. All subjects in the biomarker dataset with baseline measurement and at least one on-treatment measurement will be included in PD analyses. Predictive biomarker analyses will be performed on all subjects in the biomarker dataset with corresponding efficacy measurement.

7 STATISTICAL ANALYSES

7.1 General Methods

All analyses will be performed in SAS using version 9.2 or higher. Some figures may be generated using S-Plus.

Continuous variables will be summarized by treatment group using the mean, standard deviation, median, minimum, and maximum values. Some continuous variables may also be summarized

using the geometric mean and coefficient of variation. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100. Percentages less than 0.1 will be indicated as “< 0.1”.

In general, all analyses will be presented by tumor type and treatment group, unless otherwise specified. There will be 9 categories: NSCLC-NAIVE, MEL, SCCHN, DLBCL, NSCLC-PROG, FL, Other Solid, Other Blood, and All Comers, where sufficient data is available, unless otherwise specified.

7.2 Study Conduct

7.2.1 Study Information

Listing:

- Batch number will be listed by batch number and subject. It is noted that a subject may appear multiple times under different batch numbers.

7.2.2 Accrual

The following will be presented on the All Enrolled Subjects.

Summary:

- Number (%) of subjects enrolled and treated, by country and investigational site

Listing:

- Subjects accrued by country and investigational site

7.2.3 Relevant Protocol Deviations

A relevant protocol deviation is a deviation from the protocol which is programmed in the database and which could potentially affect the interpretability of the study results. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) will be reported through ClinSIGHT listings. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations and a listing will be provided. During the conduct of the trial, if any relevant protocol deviation is discovered that is not on this list, this SAP should be amended prior to the final database lock. Relevant protocol deviations, their implications, and subsequent actions will be reported in the CSR.

At Entrance:

- For Cohort Expansion only:
 - For the NSCLC-NAIVE cohort
 - ◆ Subjects with prior anti-PD-1/anti-PD-L1 therapy (Inclusion Criteria 2.a.ii.1.a)
 - ◆ Subjects with unknown EGFR or ALK status (Inclusion Criteria 2.a.ii.1.a)
 - For the MEL cohort
 - ◆ Subjects with prior systemic therapy for metastatic melanoma (Inclusion Criteria 2.a.ii.1.b.iv)

- ◆ Subjects with unknown BRAF V600 status (Inclusion Criteria 2.a.ii.1.b.ii)
- ◆ Subjects without histologically confirmed unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system (Inclusion Criteria 2.a.ii.1.b.iii)
- For the SCCHN cohort
 - ◆ Subjects without histologically confirmed incurable locally advanced, recurrent or metastatic SCCHN, Stage III/IV (Inclusion Criteria 2.a.ii.1.c.i)
- For the DLBCL cohort
 - ◆ Subjects without at least one lesion that is > 15 mm (1.5 cm) in the longest diameter (Inclusion Criteria 2.a.ii.1.d.v)
- For the NSCLC-PROG cohort
 - ◆ Subjects with non-squamous histology and unknown EGFR or ALK status (Inclusion Criteria 2.a.ii.1.e.iii)
 - ◆ Subjects without prior anti-PD-1/anti-PD-L1 therapy (Inclusion Criteria 2.a.ii.1.e.vi)
 - ◆ Subjects with prior anti-PD-1/anti-PD-L1 therapy with a dose date within 28 days of first dose of study therapy (Inclusion Criteria 2.a.ii.1.e.vii)
- For the FL cohort
 - ◆ Subjects without prior rituximab therapy (Inclusion Criteria 2.a.ii.1.f.i)
- Subjects without measurable disease at baseline (Inclusion Criteria 2.b)
- Subjects with baseline ECOG performance status > 1, at the screening visit only (Inclusion Criteria 2.f)
- Subjects who have previously received nivolumab, anti-CTLA4 within 100 days, or any other anti-cancer therapy within 4 weeks prior to first dose (Exclusion Criterion 1d, 3b, and 3c)

On-Treatment:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) before the last dose of study therapy
 - In the event that this occurs, this will be treated as subject's subsequent therapy for certain efficacy assessments described in [Section 4.2.1](#) (eg, BOR and DOR).
- Subjects receiving doses or frequencies that is different than what they were assigned
 - In the event that this occurs, subjects may be grouped with the actual treatment received, rather than the assigned treatment, for the analyses.
- During the first dosing visit, if subjects receive urelumab dose first, before receiving the nivolumab dose

7.3 Study Population

7.3.1 Subject Disposition

Summary:

- Screening phase: The number (%) of subjects of the following will be summarized on the population of All Enrolled Subjects.
 - All enrolled into the study
 - Entering the treatment phase
 - Enrolled but not entering the treatment phase together with the reasons
- End of treatment phase: The number (%) of subjects of the following will be summarized by treatment group and overall, based on the population of All Treated Subjects.
 - All treated subjects
 - Subjects continuing in the treatment phase
 - Subjects not continuing in the treatment phase together with the reasons
 - Subjects continuing in the study
- End of follow-up phase: The number (%) of subjects of the following will be summarized by treatment group and overall, based on the population of All Treated Subjects.
 - All treated subjects
 - Subjects continuing in the next phase
 - Subjects not continuing in the next follow-up phase together with the reasons
- End of survival follow-up phase: The number (%) of subjects of the following will be summarized by treatment group and overall, based on the population of All Treated Subjects.
 - All treated subjects
 - Subjects continuing in the survival follow-up phase
 - Subjects not continuing in the survival follow-up phase together with the reasons

Listing:

- Screen failures: Subjects who discontinued from the study pre-treatment for screen failures will be listed with the reason for screen failure
- Subject status at:
 - End of treatment phase
 - End of follow-up phase
 - End of survival follow-up phase
- Re-treatment subject status at:
 - End of re-treatment phase
 - End of follow-up phase for re-treatment eligible subjects

7.3.2 Demographics and Other Baseline Characteristics

The definition of baseline defined in [Section 6.1.1](#) will be applied here, with the exception of Viral Tumor Status among SCCHN subjects. For Viral Tumor Status, if there is a Positive finding in any baseline examination, then the subject's status will be designated as Positive.

Summary:

The following subject demographics and baseline characteristics will be summarized by treatment arm and overall using descriptive statistics or frequency statistics.

- Age (in years); age category (<65, ≥65)
- Gender
- Race
- Ethnicity (for US only)
- Height
- Baseline Weight
- Baseline ECOG status
- Disease characteristics
 - For NSCLC (both NSCLC-NAIVE and NSCLC-PROG): stage at initial diagnosis and at study entry, cell type, EGFR mutation status, ALK translocation status, tobacco use status, electronic cigarette use status, PD-L1 level
 - For MEL: stage and M status at initial diagnosis and at study entry, subtype of disease, BRAF mutation status, PD-L1 level
 - For SCCHN: stage at initial diagnosis and at study entry, cell type, location, viral tumor status
 - For DLBCL and FL: stage at initial diagnosis and at study entry, IPI score
 - For tumor types that are not NSCLC-NAIVE, MEL, SCCHN, DLBCL, NSCLC-PROG, and FL, the diagnosis will be presented in a frequency table, along with their stage at study entry

Listing:

- All relevant data, generally variables listed above
- General medical history
- Tobacco use, electronic cigarette use, and alcohol use
- Relevant factors
- Potential risk factors
 - For Pulmonary related events
 - For Hepatobiliary related events

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the population of All Treated Subjects “as treated” as described in [Section 6.2](#).

The urelumab and nivolumab combination will be given on Days 1 and 29 in 8 week cycles for 6 cycles. The cycle start date will correspond to the dosing date. Calculations below excludes the re-treatment period.

7.4.1 Study Therapy

Summary:

- Number (%) of treated subjects exposed for specified periods of time such as less than 1 week, 1 week to 1 month, 1 month to 6 months by treatment group.
- Descriptive statistics will be provided by treatment group for the following.
 - Urelumab
 - ◆ Number of doses of Urelumab
 - ◆ Duration of therapy (weeks) of Urelumab = (last dose date - first dose date + 28)/7
 - ◆ Cumulative dose (mg) of Urelumab = the sum of all actual doses that a subject received
 - ◆ Dose intensity (mg/wk) = cumulative dose (mg) / duration of therapy (weeks)
 - ◆ Relative dose intensity (%) = (dose intensity / planned dose)*100
 - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
 - Nivolumab
 - ◆ Number of doses of Nivolumab
 - ◆ Duration of therapy (weeks) of Nivolumab = (last dose date - first dose date + 14)/7
 - ◆ For subjects enrolled prior to Protocol Amendment 03:
 - Cumulative dose (mg/kg) of Nivolumab = the sum of all actual doses that a subject received
 - Dose intensity (mg/kg/wk) = cumulative dose (mg/kg) / duration of therapy (weeks)
 - ◆ For subjects enrolled after Protocol Amendment 03:
 - Cumulative dose (mg) of Nivolumab = the sum of all actual doses that a subject received
 - Dose intensity (mg/wk) = cumulative dose (mg) / duration of therapy (weeks)
 - ◆ Relative dose intensity (%) = (dose intensity / planned dose)*100
 - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Listing:

- Drug administration
- Number of doses, duration of therapy, cumulative dose, dose intensity, and relative dose intensity

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by treatment group.

- Urelumab
 - Number (%) of subjects with dose delay and discontinuation along with the reason
 - Infusion interruptions

- *More than one reason or one interruption per patient may be counted in these statistics

- All relevant information on dose modification listed above

[illegible]

[illegible]

group. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized based on the actual data and will be described in each deliverable's DPP. An example of the categories are: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 120-150 days, 151 or more days.

Figure:

The following will be plotted by tumor type and treatment group.

- Percent change from baseline in target lesion tumor burden over time (ie, spider plot)
- Best percent change from baseline in target lesions (ie, waterfall plot)
- Kaplan-Meier plot of DOR for responders only
- Swimmer plot of DOR, and time on therapy for responders only
- Kaplan-Meier plot of PFS
- Kaplan-Meier plot of OS

Listing:

The following will be listed by tumor type and treatment group.

- Tumor lesion measurements
- Tumor evaluation at each visit, including non-target lesions and new lesions, tumor change from smallest sum of diameters in target lesions, and corresponding change (or percent change) from baseline
- Subject level efficacy for All Treated Subjects: BOR, OS, PFS, best response in target lesions, death indicator, duration of response for responders
- Survival - survival status, first dose date, last dose date, last known alive date, death date, time to death

7.5.1 Other Observations Related to Efficacy

Summary:

- Certain efficacy analyses in [Section 7.5](#) are expected to be repeated by mutation status (eg, EGFR, BRAF), HPV status, IPI score, or other clinically meaningful disease characteristic, if there are sufficient data. These will be detailed in the DPP.

Figure:

- Certain efficacy plots may also be plotted by mutation status (eg, EGFR, BRAF), HPV status, IPI score, or other clinically meaningful disease characteristic, if there are sufficient data

Listing:

- FDG-PET
- Bone Marrow

7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by tumor type, treatment arm and overall. Deaths and SAEs will be listed using All Enrolled Subjects.

Adverse events will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock and the severity will be graded using the NCI CTCAE version 4.0. Drug-related AEs are those events with relationship to study drug “Related” as recorded on the Case Report Form (CRF). If the relationship to study drug is missing, the AE will be considered as drug-related.

Listing of AEs will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of AEs will include (1) events occurring from the first dose date to 100 days (inclusive) after the last dose of either study drug for subjects who are off study treatment and (2) all events occurring from first dose date for subjects who are still on study medication, excluding the re-treatment period.

All recorded AEs will be listed and tabulated by system organ class (SOC), preferred term (PT), treated arm, and dose. When reporting AEs by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the PT level, (2) once at the SOC level, and (3) once in the ‘Total subject’ row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.0) grade. Summaries of laboratory results include baseline and (1) post-baseline results up to 100 days (inclusive) after the last dose of either study drug for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication, excluding the re-treatment period.

7.6.1 Deaths

Summary:

- All deaths during the study within 100 days after the last dose of either study drug will be summarized for cause of deaths by treatment group.

Listing:

- All recorded deaths for All Enrolled Subjects will be listed

7.6.2 Other Serious Adverse Events

Summary:

The following will be summarized by tumor type, treatment arm and overall.

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:

- By-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapies

Adverse events leading to study drug discontinuation are AEs with action taken as “Drug was discontinued”.

Summary:

The following will be summarized by tumor type treatment arm and overall.

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.
- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:

- By-subject AEs leading to discontinuation listing will be provided.

7.6.4 Overall Adverse Events

Summary:

Adverse events and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise. The following will be summarized by tumor type, treatment arm and overall.

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment arm.
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of any non-serious AEs presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment arm.

Listing:

- All recorded AEs occurring in the pretreatment, on-treatment, and post treatment period will be listed.

7.6.5 Events of Special Interest

The events of special interest (EOSI) consist of a list of preferred terms grouped by specific categories (endocrinopathies, infusion reactions, gastrointestinal, hepatobiliary, pulmonary,

renal, skin). These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Changes may be made to this list with each new version of MedDRA and the final list used for the CSR will be included in an Appendix of the CSR.

Summary:

The following will be summarized by tumor type, treatment arm and overall.

- Overall summary of any EOSI by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5).
- Overall summary of drug-related EOSI by worst CTC grade presented by Category/ PT (any grade, grade 3-4, grade 5).
- Overall summary of any serious EOSI by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5).
- Overall summary of any EOSI leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5).
- Overall summary of drug-related EOSI leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5).

Listing:

- EOSI definition
- Listings for the EOSI will be provided by subject and dose.

7.6.6 Multiple Events

Analyses that take into account the multiple occurrences of a given AE will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms⁹ in order to collapse AE records into unique records based on the PT. This data will be presented as the rate per 100 person-years. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of AE follow-up that is based on exposure to the study medication. The person-year exposure will be computed as the sum over the subjects' follow-up expressed in years and is defined as:

- Date of last dose of study treatment - date of first dose of study treatment + 100 +1 days, for subject who are off study treatment and were followed for at least 100 days after last dose of study medication.
- Last known date alive - date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 days after last dose of study medication.

When specified, the 95% CI of the rate per 100 person-years of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless¹⁰.

Summary:

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs.

- For EOSI:
 - Frequency of unique AEs, meaning the number of subjects experiencing an AE once or multiple times by tumor type, treatment arm, and overall

Listing:

- Unique instances of all AEs, ie, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (ie, same PT) have been collapsed.

7.6.7 Clinical Laboratory Evaluations

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses may be repeated using US conventional units. In addition, further analyses on specific laboratory parameters will be performed by treatment group and is described in Sections 7.6.7.1 and 7.6.7.2.

Summary:

The number (%) of subjects with the following will be summarized by tumor type, treatment group and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Shift-table of worst on-study CTC grade compared to baseline CTC grade

Listing:

- A by-subject listing of these laboratory parameters will be provided.
- Laboratory abnormality criteria
- Laboratory results outside of normal range

7.6.7.1 Abnormal Hepatic Function Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by tumor type, treatment group, and overall.

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

Figure:

The following scatter plots will be produced for the following hepatic laboratory parameters. On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

- Total bilirubin peak vs. AST peak
- Total bilirubin peak vs. ALT peak

Listing:

- A by-subject listing of these specific abnormalities will be provided.

7.6.7.2 Abnormal Thyroid Function Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by tumor type, treatment group, and overall.

- TSH value $>$ ULN and
 - with baseline TSH value \leq ULN
 - at least one T3/T4 test value $<$ LLN
- TSH $<$ LLN and
 - with baseline TSH value \geq LLN
 - at least one T3/T4 test value $>$ ULN

Listing:

- A by-subject listing of these specific abnormalities will be provided.

7.6.7.3 Other Observations Related to Laboratory Values

- Time to onset Liver Function Test (LFT) elevation
- Time to onset LFT from latest dose
- Time to onset Thrombocytopenia
- Time to onset Neutropenia
- Time to resolution of LFT from first dose
- Time to resolution of Neutropenia
- Time to resolution of Thrombocytopenia
- Steroid use % of subjects
- LFT elevation Hepatotox medication use
- Patients with Neutropenia grade ≥ 2 and GCSF treatment
- Neutropenia grade ≥ 2 and temp elevation
- Patients with simultaneous occurrence of toxicity elevations

7.6.8 Electrocardiograms

Listing:

- A by-subject listing of all ECG measures
- A listing of only abnormal ECG interpretations

7.6.9 Vital Signs and Physical Findings

Summary:

The following parameters and their corresponding change from baseline will be summarized by timepoint and treatment group.

- Vital Signs

- Body weight and performance status

Listing:

- Vital Signs
- Height, body weight and performance status
- Abnormal physical examination findings

7.6.10 Other Observations Related to Safety

Listing:

The following by-subject listings will be produced if data exists.

- Pulse Oximetry
- Abnormal Chest X-Ray
- Abnormal Bone Scan
- Abnormal Brain Scan
- Diagnostic and medical procedures
- Pregnancy

7.7 Pharmacokinetic Analyses

The PK parameters and concentration data of urelumab and nivolumab will be summarized and listed by tumor type, treatment arm and sampling time. PK concentrations may be used in combination with other studies for exposure-response or population PK modeling, which will be part of a separate report.

7.7.1 Pharmacokinetic Concentrations

Summary:

Summary statistics will be provided for the following pharmacokinetic serum concentrations by tumor type, dose, regimen, study day and time based on the Urelumab PK Subjects and Nivolumab PK Subjects.

- Serum concentrations of Urelumab
- Serum concentrations of Nivolumab

Figure:

Plots of the following concentration vs. cycle by dose and regimen

- Serum concentrations of Urelumab
- Serum concentrations of Nivolumab

Listing:

- Urelumab and nivolumab serum concentrations

7.7.2 Pharmacokinetic Parameters

Summary:

Summary statistics will be provided for the following parameters by tumor type, dose, regimen, study day and time based on the Urelumab PK Subjects and Nivolumab PK Subjects, where data is available. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(TAU), and Ctrough. Median, minimum, and maximum will be presented for Tmax.

- Cmax
- Tmax
- AUC(0-T)
- AUC(TAU)
- Ctrough
- Coeinf

Figure:

Scatter plots of the following parameters vs. cycle by dose and regimen

- Ctrough
- AUC(TAU)

Listing:

- Urelumab and nivolumab PK concentrations
- Urelumab and nivolumab PK parameters



[REDACTED]

Category	Percentage
Very important	10%
Important	25%
Not important	45%
Don't know	20%
Other	0%
Refused	0%
Non-response	0%

██████████

1. [REDACTED]

114

36

[REDACTED]

8 CONVENTIONS

Safety data will be handled according to the BMS safety data conventions¹¹.

The following conversion factors will be used to convert days to months or years.

- 1 month = 30.4375 days
- 1 year = 365.25 days

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report and other interim analyses will be given in the Data Presentation Plan.

