Official Title of Study:

A Phase 2, Open-label, Single-arm, Two-cohort Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) or Relapsed/Refractory Primary Testicular Lymphoma (PTL)

NCT Number: NCT02857426

Document Date (Date in which document was last revised): February 9, 2018

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 2, OPEN-LABEL, SINGLE-ARM, TWO-COHORT STUDY OF NIVOLUMAB IN RELAPSED/REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) OR RELAPSED/REFRACTORY PRIMARY TESTICULAR LYMPHOMA (PTL)

CHECKMATE 647: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION

PROTOCOL CA209-647

VERSION # 1.0

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[redacted]

Research Hypothesis:

Treatment with nivolumab will demonstrate clinically meaningful efficacy in subjects with relapsed/refractory PCNSL or PTL.

Schedule of Analyses:

The analysis of the primary endpoint in each cohort will occur at least 6 months after last patient first treatment in each cohort. Secondary endpoints will be analyzed at the same time as the primary endpoint.

2 STUDY DESCRIPTION

2.1 Study Design

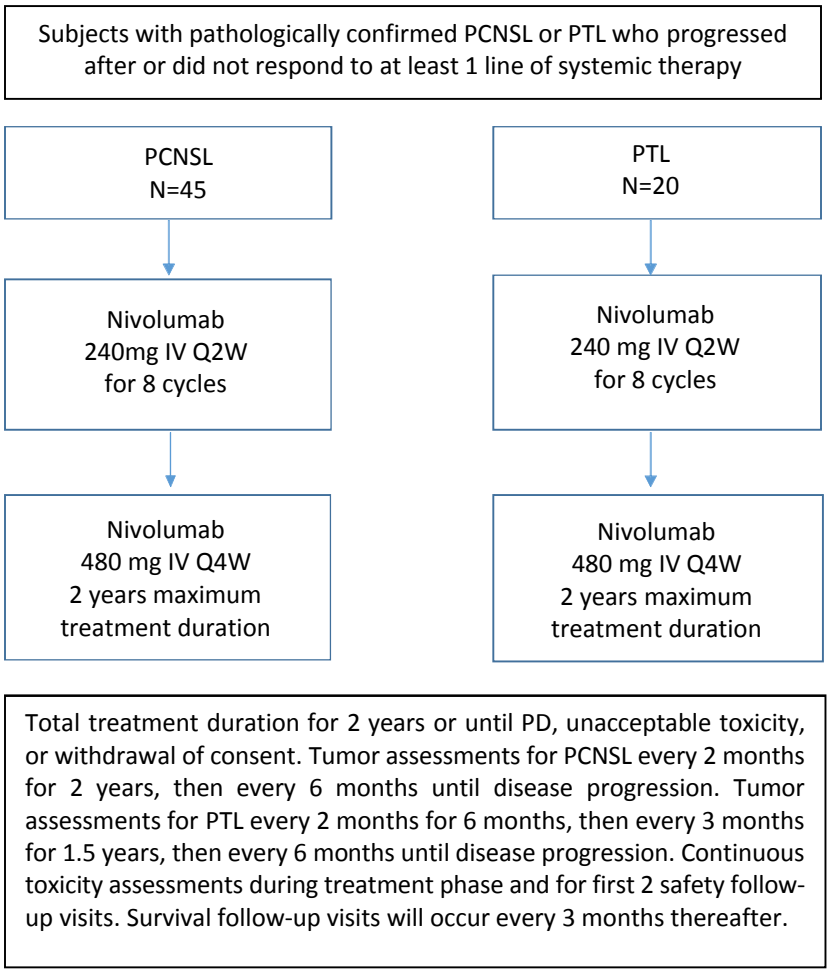
CA209647 is a Phase 2, open-label, single-arm, 2-cohort study to estimate the safety and efficacy of nivolumab in participants with relapsed/refractory PCNSL or PTL. Nivolumab 240 mg will be given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg will be given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab will be administered as a 30-minute infusion. A finite treatment duration with immune therapies in this patient population remains an area of ongoing research; therefore the treatment duration chosen was 2 years.

The study will further characterize safety and evaluate the antitumor activity of nivolumab in participants with relapsed/refractory PCNSL or PTL who progressed after or did not respond to at least 1 line of systemic therapy.

The primary endpoint is BICR-assessed ORR, and will be analyzed 6 months after last patient first treatment in each cohort.

This study will consist of 3 phases: screening, treatment, and follow-up. The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design



2.2 Treatment Assignment

Participants will be identified and informed consent obtained. Participants must be enrolled into the study by the interactive web response system (IVRS) to obtain the participant number. The investigator or designee will register the participant for enrollment by following the procedures established by BMS.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Change
Revised Protocol 04	29-Nov-2017	To characterize nivolumab pharmacokinetic [redacted] in the cerebrospinal fluid (CSF), lumbar puncture(s) (optional) have been added and will be obtained from consenting patients with relapsed/refractory PCNSL or relapsed/refractory PTL with CNS involvement. [redacted]
Administrative Letter 06	04-Sep-2017	Corrected the Appendix 6 of the protocol (Tumor Flare; Treatment strategies during TF) by removing the CTCAE classification of cerebral edema.
Revised Protocol 03	07-Apr-2017	Incorporates Amendment(s) 09
Amendment 09	07-Apr-2017	Changes to eligibility - To allow enrollment of subjects with PTL who undergo orchiectomy - To allow enrollment of subjects with PTL with measurable nodule disease - To specify more precisely the first line of therapy in PCNSL and PTL - To exclude subjects with significantly increased risk for bleeding complications - To lower the dose of dexamethasone or equivalent allowed 14 days prior to first dose of nivolumab to less than or equal to 2mg/day. The use of CT Scans without PET scans will not be allowed for assessment for subjects with PTL. Added the possibility for administrative interim analyses. Recommendations for the management of Tumor Flare have been added as Appendix 6. Incorporates changes per Administrative Letters 04, 03, and 02.
Administrative Letter 04	07-Feb-2017	Change Medical Monitor address.
Administrative Letter 03	17-Nov-2016	To further clarify protocol requirements for tumor tissue submission at screening and correct typographic errors in Table 5.1-2 of the protocol.
Administrative Letter 02	20-Oct-2016	Clarify the protocol requirements for tumor tissue submission at screening.
Revised Protocol 02	05-Oct-2016	Incorporates Amendment(s) 05
Amendment 05	05-Oct-2016	To reflect update in the treatment management algorithms to be consistent with the updated nivolumab investigator brochure (IB) V15, updates to the acceptable methods of contraception in order to be consistent with the most recent version of BMS SOP and IB V15. To allow the enrollment of patients with PCNSL that cannot produce a minimum of 25 slides [redacted]

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Change
		[redacted] Other changes were made to resolve minor inconsistencies or to provide clarifications.
Revised Protocol 01	22-Jun-2016	Incorporates Amendment(s) 01
Amendment 01	22-Jun-2016	Subjects in the cohorts with PCNSL and PTL with brain and or spinal lesions are allowed to enroll if they are on 4 mg per day or less of dexamethasone. Subjects who had undergone allogeneic stem cell transplant > 12 months prior to first dose of study drug, have no evidence of active graft versus host disease, and are not on systemic immunosuppressive therapy are allowed to participate in the study. Neurologic Assessment in Neuro-Oncology (NANO) has been incorporated in the exploratory endpoints in the protocol. If the dose of dexamethasone is increased during the screening period following the screening MRI, and if there is clinical worsening in neurological symptoms following the MRI, the MRI must be repeated. Due to the rapidly progressing nature of CNS tumors, a brain MRI is to be performed within 14 days before the first dose of study treatment in both cohorts in order to accurately reflect the disease burden. Language was added for the collection of prospective blood samples, and for BMS to retain residual blood and tissue samples, so that scientists can perform additional research. Incorporation of other minor changes to correct and/or clarify protocol requirements.

2.5 Data Monitoring Committee

Not applicable.

3 OBJECTIVES

3.1 Primary Objective

To assess the clinical benefit of nivolumab in subjects with relapsed/refractory PCNSL or relapsed/refractory PTL as measured by ORR by blinded Independent Central Review (BICR).

3.2 Secondary Objectives

- To assess progression free survival (PFS) based on BICR assessment for PCNSL or PTL, respectively

- To assess ORR and duration of response (DOR) based on investigator assessment for PCNSL or PTL, respectively
- To assess overall survival (OS) for PCNSL or PTL, respectively

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint(s)

The primary objective will be measured by the primary endpoint of BICR-assessed ORR. It is defined as the number of participants with a best overall response (BOR) of CR, unconfirmed complete response (CRu) or PR, based on the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, divided by the number of treated participants within each cohort.

The BICR-assessed BOR is defined as the best response designation recorded between the date of first study drug dose and the date of initial objectively documented progression per criteria or the date of subsequent therapy, whichever occurs first. For purposes of analysis, if a participant receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this participant will be counted in the denominator (as non-responder).

The BICR-assessed objective response will be further characterized by the time to response (TTR) and duration of response (DOR).

TTR is defined as the time from first dosing date to the date of the first response, based on BICR assessment. TTR will be evaluated for responders only.

DOR is defined as the time from first response (CR, CRu or PR) to the date of initial objectively documented progression as determined using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first. For participants who neither progress nor die, the DOR will be censored on the date of their last tumor assessment. Participants who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior or on the first subsequent anticancer therapy date. The censoring scheme of DOR will be the same as the primary censoring scheme for PFS. This endpoint will only be evaluated in participants with objective response of CR, CRu or PR.

4.2 Secondary Endpoint(s)

4.2.1 Progression Free Survival Based on BICR Assessment

PFS is defined as the time from first dosing date to the date of the first documented progression using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first. Participants who die without a reported progression and did not start a subsequent therapy will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last tumor assessment. Participants who did not have any on study assessments and did not die will be censored on the first dosing date. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The censoring scheme is summarized in Table 4.2.1-1.

Table 4.2.1-1: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First dosing date	Censored
No on-study tumor assessments and no death	First dosing date	Censored
New subsequent anticancer therapy started without a prior reported progression by IPCG/Lugano 2014 criteria	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Progression per IPCG / Lugano 2014 criteria documented at a scheduled or unscheduled visit and no subsequent anticancer therapy started before	Date of the first documented tumor progression per IPCG/Lugano 2014 criteria	Progressed

Table 4.2.1-1: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
Participant progression free, no death and no subsequent anti-cancer therapy started	Date of last evaluable tumor assessment per IPCG/Lugano 2014 criteria	Censored
Death without prior progression per IPCG/ Lugano 2014 criteria and no subsequent anticancer therapy started	Date of death	Progressed

4.2.2 Objective Response Rate and Duration of Response Based on Investigator Assessment

Investigator-assessed ORR and DOR are defined similarly as described for ORR and DOR per BICR assessment above, but will be assessed per investigator.

4.2.3 Overall Survival

Overall Survival (OS): defined as the time between the first dosing date and the date of death. Participants who are alive at the time of analysis will be censored at last known alive date (LKAD). The overall survival rate at time T is defined as the probability that a subject is alive at time T following first dosing date.

[redacted]

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The planned sample size for this study will be approximately 65 treated participants, placed into 2 cohorts of participants: PCNSL (N = 45), and PTL (N = 20).

In addition, Table 5-1 summarizes the 95% exact confidence interval (CI) for the target ORRs ranging from 28.9% to 60% with sample size of 20 and 45. At observed ORR ≥ 28.9% with 45 PCNSL participants, the lower bound of the 95% CI excludes the historical response rates in of 14% in recurrent primary central nervous system lymphoma. At observed ORR ≥ 40% with 20 PTL participants, the lower bound of the 95% CI excludes the response rate of 14%.

The sample size for the PCNSL cohort was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in PCNSL through observation of less common safety events. In particular, administration of nivolumab to 45 participants provides 90% probability of observing at least 1 occurrence of any AE that would occur with 5% incidence in the population from which the sample is drawn.

Table 5-1: Observed ORR with Exact 95 % CI

N	ORR	95% Exact CI
20	30%	[11.9% - 54.3%]
	35%	[15.4% - 59.2%]
	40%	[19.1% - 63.9%]
	50%	[27.2% - 72.8%]
	60%	[36.1% - 80.9%]
45	28.9%	[16.4% - 44.3%]
	40.0%	[25.7% - 55.7%]
	51.1%	[35.8% - 66.3%]
	60%	[44.3% - 74.3%]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

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 day of the first dose of study treatment

- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment.

If there are multiple valid assessments, the assessment that is closest to day (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), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

See Core Safety SAP.

6.2 Treatment Regimens

All participants will be treated with nivolumab 240 mg, given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg will be given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent.

6.3 Populations for Analyses

Within each cohort the following populations will be defined.

- **All enrolled participants**: All participants who signed an informed consent form and were registered into the IVRS.
- **All treated participants**: All participants who received at least one dose of study medication. This is the primary dataset for efficacy and safety.
- **All treated participants enrolled pre-amendment 9**: All treated participants who signed their informed consent before protocol amendment 9 (up to March 24, 2017).
- **All treated participants enrolled post-amendment 9**: All treated participants who signed their informed consent after protocol amendment 9 (after March 24, 2017).
- All treated participants with high dose corticosteroids at baseline: All treated participants who received > 2mg per day of dexamethasone equivalent within 14 days prior first Nivolumab dose date.
- All treated participants without high dose corticosteroids at baseline: All treated participants who received ≤ 2mg per day of dexamethasone equivalent within 14 days prior first Nivolumab dose date.

- **Response evaluable participants**: All treated participants who have baseline and at least one on-study evaluable tumor measurement.
- [redacted]
- **Serum PK participants**: All participants with available serum concentration time data from participants dosed with nivolumab
- **CSF PK participants**: All participants with available CSF concentration time data from participants dosed with nivolumab
- **Immunogenicity evaluable participants**: All treated participants with baseline and at least 1 post baseline immunogenicity assessment
- **Outcomes research participants**: All treated participants who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (separately for each outcome research measure EuroQol (EQ)-5D-3L scoring function, QLQ-C30, QLQ-BN20 and NANO).
- **Nivolumab participants treated beyond progression:** All participants who received at least one dose of nivolumab after the date of initial progression based on investigator assessment.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of participants falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by cohort (with total) using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (e.g., progression free survival, overall survival and duration of response) will be estimated using Kaplan Meier techniques. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t)[5,6]. Rates at fixed time points (e.g., PFS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t)[7].

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[1].

All analyses will be performed separately for each cohort upon completion of follow-up for the primary endpoint in each cohort. There will be no

multiplicity adjustment for p-values.

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized on the enrolled population:

- Number of participants accrued by country and investigational site
- Number of participants accrued by month

A by participant listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At entrance:

- Participants without measurable disease at baseline
- Participant with baseline Karnofsky performance status < 70
- Participants with pathologically confirmed PCNSL or PTL who didn't meet the eligibility criteria of progressing after or not responding to at least 1 line of systemic therapy
- For subjects enrolled afterprotocol amendment 9, patients had more than 2mg/day dexamethasone equivalent in the 14 days prior to the first nivolumab dose

On-Study:

- Participants receiving concurrent anti-cancer therapy (systemic, surgery, non-palliative radiotherapy, transplant) other than nivolumab.

A summary table and a by participant listing of relevant protocol will be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of participants enrolled (treated or not) will be presented along with the reason for not being treated.

Number of participants who discontinued treatment along with corresponding reason will also be tabulated.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all treated participants. All baseline presentations will identify participants with missing measurements.

- Age (descriptive statistics)

- Age categories (< 30, ≥ 30 and < 45, ≥ 45 and < 60, ≥ 60)
- Gender (male, female)
- Race (white, black or african american, asian, american indian or alaska native, native hawaiian or other pacific islander, other)
- Baseline Karnofsky Performance Status (median and range, ≥ 90, ≥ 70 and < 90, < 70)
- Weight (descriptive statistics)
- Time from initial disease diagnosis to first dose of study medication (median, range, < 3 months; ≥ 3 months)
- Region (US/Canada, Europe, Rest of the World)
- Smoking Status (Yes, No, Unknown)
- Disease stage at initial diagnosis (PTL cohort only) (stage 1 or 2, 3, 4, unknown)
- Disease status at study entry (relapsed, refractory, or relapsed and refractory)
- CNS involvement at study entry (PTL cohort only) (Yes, No, unknown)
- Ocular involvement (Yes, No, unknown)
- All lesions (Investigator Tumor Assessments at Baseline): sites of diseases, number of disease sites per participant
- Target Lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of product diameters of target lesions.

The same analysis would be performed by subjects enrolled pre- vs. post-amendment 9 for PCNSL cohort as well as by subjects high dose versus low dose of corticosteroids at baseline.

7.3.3 Medical history- Concurrent diseases

General medical history will be listed by participant and pretreatment events will be tabulated.

7.3.4 Prior therapy agents

For participants with PCNSL, prior therapy includes high-dose methotrexate (HD-MTX), HD-MTX-based regimen, high-dose cytarabine, radiation therapy alone as treatment or as part of consolidation therapy, high-dose therapy with autologous stem cell transplant as part of consolidation therapy, and/or intraocular MTX alone or as part of consolidation therapy.

For participants with PTL, prior therapy includes chemo-immunotherapy (e.g., CHOP-R or any other regimens), with/without prophylactic RT to contralateral testis or orchiectomy or intrathecal chemotherapy.

The following will be summarized for PCNSL and PTL (as appropriate):

- Number of participants who received Prior Systemic Cancer Therapy by type (such as but may not be limited to Immunotherapy by Monoclonal Antibodies, Steroid, Chemotherapy – Other than anthracyclines, Chemotherapy - Anthracyclines, Kinase Inhibitors, Immunomodulary Derivatives, Radioimmunotherapy, Other)
- Number of participants by type of regimen for first and second lines of therapy

- Number of lines of prior systemic therapies received (median, range, 1, 2, 3, 4, ≥ 5)
- Time from completion of most recent prior regimen to treatment (median, range, < 3, 3 - 6, > 6 months)
- Prior radiotherapy (yes or no, not reported)
- Prior orchiectomy (yes or no, not reported)
- Prior autologous transplant (Yes, No, Not reported)
- Prior allogeneic transplant (Yes, no, Not reported)
- Prior surgery related to cancer (Yes, No, Not reported)

Other Prior therapy:

- Prior/current non-study medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. A listing by participant will also be provided.

7.3.5 Baseline examinations

Participants with abnormal baseline physical examination will be tabulated by examination criteria and by cohort.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated participants.

7.4.1 Administration of study therapy

The following parameters will be summarized (descriptive statistics):

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received (summary statistics)
- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for participants who discontinued study therapy. Participants who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.
- A by-participant listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Table 7.4.1-1: Administration of study therapy: definition of parameters

	nivolumab
Dosing schedule per protocol	240mg Q2W for first 8 cylces; 480 Q4W starting cycle 9
Dose	Dose mg is defined as Total Dose administered (mg). Dose administered in mg at each dosing.

Table 7.4.1-1: Administration of study therapy: definition of parameters

	nivolumab
Cumulative Dose	Cum dose (mg) is sum of the doses (mg) administered to a participant during the treatment period.
Cumulative Planned Dose	For subjects who only receive 240mg Q2W up to cycles 8, cumulative planned dose in cycles 1-8 is (min(Last dose date within cycles 1-8 + 14 day, death date) - Start dose date) x 480mg / 28 day For subjects receive 480 Q4W starting cycle 9, cumulative planned dose from cycle 9 is (min(Last dose date + 28 day, death date) - Start dose date of cycle 9) x 480mg / 28 day
Relative dose intensity (%)	Cum dose /Cumulative Planned Dose x 100
Duration of treatment	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose delays

7.4.2.2 Dose delays

Treatment may be delayed for up to a maximum of 6 weeks from the last dose. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). Length of delay is defined as (duration of previous cycle in days - 14). Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 43, ≥ 43 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized:

- Number of participants with at least one dose delayed, number of dose delayed per participant, Length of Delay and Reason for Dose Delay

7.4.2.3 Infusion Interruptions and Rate Changes

The following parameters will be summarized:

- Number of participants with at least one dose infusion interruption, number of infusion interruptions per participant and the reason for interruption.
- Number of participants with at least one IV infusion rate reduction, number of IV infusion rate reduction per participant and the reason for reduction

7.4.2.4 Dose Reductions/Escalation

There will be no dose escalations or reductions of nivolumab allowed.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (participants with any concomitant medication, participants by medication class and generic term).
- Median and range of corticosteroids

A by-participant listing will accompany the tables.

7.5 Efficacy

Unless specifically mentioned, all efficacy analyses will be performed by two cohorts separately.

7.5.1 Primary analysis on BICR-assessed ORR

The BICR-assessed ORR will be summarized by cohort for all treated participants by a binomial response rate. The Clopper-Pearson method[1] will be used to estimate the two-sided 95% confidence interval.

Best overall response (BOR) will be summarized by response category (CR, CRu, PR, SD, PD, Non-evaluable, and not reported).

To assess tumor response kinetics, time to response will be analyzed using the KM methodology for all treated participants by cohort. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time to response + 1 day of all participants in that cohort.

The BICR-assessed DOR will be summarized by cohort for participants who achieve PR, CRu or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CIs (based on the log-log transformation) and range, will also be calculated.

The following participant-level graphics will also be provided by cohort:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response evaluable participants, a waterfall plot showing the best reduction in target lesion will be produced. A spider plot showing the percentage of tumor size changes over time will also be produced.

The efficacy assessment slit lamp examination including the CNS ocular involvement over time relative to the 1st and the last doses will be listed. This may only includes patients with CNS ocular involvement at baseline.

7.5.2 Secondary Efficacy Endpoints

7.5.2.1 PFS assessed by BICR

The BICR-assessed PFS assessment will be summarized descriptively by cohort using the Kaplan-Meier (KM) product-limit method for each cohort. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.

The BICR-assessed PFS rates at 3 and 6 months will be estimated using KM estimates on the PFS curve. PFS rates at 9, 12, 18, 24, 36 months may also be estimated depending on whether minimum follow-up will be longer than or equal to timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

The source of the BICR-assessed PFS event (death vs. progression) will be summarized. The status of participants who are censored in the PFS Kaplan-Meier analysis will be tabulatedusing following categories:

- On-study (on treatment or progression-free in follow-up).
- Off-study: (lost to follow-up, withdraw consent other).
- Received subsequent anti-cancer therapy.

PFS assessed by investigator will be analyzed similarly to the BICR assessed PFS.

7.5.2.2 ORR, BOR, TTR and DOR by investigator

The ORR, BOR, TTR and DOR assessed by investigator will be analyzed similarly to the same endpoints assessed by BICR.

7.5.2.3 Overall Survival (OS)

The OS curves will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t).

Survival rates at 3, 6, 9, 12, 18, 24, 36 months may also be estimated using KM estimates on the OS curve for each cohort. Minimum follow-up must be ≥ timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood's formula for variance derivation and on log-log transformation applied on the survivor function S(t).

The status of participants who are censored in the OS Kaplan-Meier analysis will be tabulated using following categories:

- On-study (on-treatment or in follow-up).
- Off-study (lost to follow-up, withdraw consent, etc.).

7.5.2.4 Efficacy Analyses for Both PFS and OS

Participant Follow-up

The minimum follow-up will be reported. The minimum follow-up is defined as the time interval between the last patient's first dosing date of the considered cohort and the clinical cutoff date.

The extent of follow-up defined as the time between first dosing date and last known date alive (for participants who are alive) or death date (for participants who died) will be summarized descriptively (median, min, max) for all treated participants.

The currentness of follow-up, defined as the time between last OS contact (i.e., last known date alive or death date) and data cut-off date, will be summarized. Participants who died before data cut-off date will automatically have zero value for currentness of follow-up. For participants 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 into the following categories: 0 days, 1-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

Follow-Up Therapy

The following information pertaining to subsequent therapies will be summarized:

Number and percentage of participants receiving subsequent therapies including:

- Chemotherapy by drug name.
- Immunotherapy (anti-PD1 agents, anti-CTLA4 agents and others, by drug name).
- Other investigational agent by drug name.
- Surgery.
- Radiotherapy.
- Autologous transplant
- Allogeneic transplant

A participant listing of follow-up therapy will be produced for participants who had any subsequent therapy.

By-subject listings will be provided for study related procedures including eye fundus examination, eye stereo color fundus photography, lumbar puncture, and lymphoma pet scan.

For subjects who underwent subsequent allogeneic transplant, by-subject listings will be provided with the following information: transplant characteristics, best response to transplant, GVHD, characteristics of acute GVHD and other transplant complications.

7.5.2.5 Efficacy for Participants Treated Beyond Progression

Individual time course of tumor burden change from baseline in target lesions, per investigator, will be generated for nivolumab participants treated beyond progression (spider plot).

The duration of treatment and number of doses beyond progression will be summarized.

7.5.3 Subset Analyses

The influence of enrolment prior versus after protocol amendment 9 and the influence on high versus lowdose of dexamethasone prior to the first dose of nivolumab on the efficacy measures will be evaluated descriptively by analyzing the following efficacy endpoints on each subset:

- BICR-assessed best overall response (BOR) will be summarized by response category (CR, CRu, PR, SD, PD, Non-evaluable, and not reported).
- BICR-assessed time to response (TTR) will be analyzed using the KM methodology.
- BICR-assessed DOR will be summarized for participants who achieve PR, CRu or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CIs (based on the log-log transformation) and range, will also be calculated.
- The BICR-assessed PFS assessment will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.
- The OS curves will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t).

To study the effect of steroid use at baseline, objective response status (responder vs non-responder) may be modeled by a logistic regression with baseline steroid use as a continuous variable. For PFS and OS, a Cox proportional hazards model with baseline steroid use as a continuous variable may be applied.

7.5.4 Interim Analysis

Not applicable.

7.6 Safety

A subset of tables and listings from the Core Safety SAP will be analyzed. Details will be included in the DPP.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Immune Modulating Medication

See Core Safety SAP.

7.6.8 Multiple Events

See Core Safety SAP.

7.6.9 Other Events of Special Interest

7.6.10 See Core Safety SAP.Immune-Mediated Adverse Events

See Core Safety SAP.

7.6.11 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated participants who underwent that laboratory test.

7.6.11.1 Hematology

See Core Safety SAP.

7.6.11.2 Serum Chemistry

See Core Safety SAP.

7.6.11.3 Electrolytes

See Core Safety SAP.

7.6.11.4 Additional Analyses

See Core Safety SAP.

7.6.12 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.6.13 Immunogenicity Endpoints

See Core Safety SAP

7.6.14 Pregnancy

See Core Safety SAP.

7.6.15 Adverse Events by Subgroup

See Core Safety SAP.

7.7 Pharmacokinetics

The listing of concentration of nivolumab in CSF and in serum will be provided in CSR.

The nivolumab concentration data in serum or in CSF obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for exposure-response analyses. Results of population PK and exposure response-analyses would be reported separately outside of the study CSR.

[redacted]

7.9 Outcomes Research Analyses

The outcome research analyses will be performed using all outcome research participants.

7.9.1 EQ-5D-3L questionnaire

Participant's overall health state on a visual analog scale (EQ-VAS) at each assessment time point and change from baseline will be summarized using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles, minimum, maximum) by cohort.

Proportion of participants reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem by cohort. Percentages will be based on number participants assessed at assessment time point.EQ-5D questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., number of participants on treatment or in follow up), will be calculated along with reason for the questionnaire not completed and summarized for each assessment time point by cohort.A by-participant listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

7.9.2 EORTC-QLQ-C30

Baseline measures will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each QLQ-C30 item, as well as global and functional scales by cohort, based on participants with a baseline measurement.

Post-baseline time point measures and change from baseline will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for global, functional, and symptom scales at each assessment time point by cohort. This analysis will be performed in participants who have an assessment at baseline and at least one on-study assessment.

EORTC-QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., number of participants on treatment or in follow up), will be calculated along with reason for the questionnaire not completed and summarized for each assessment time point by cohort.

A by-participant listing containing all single items on the questionnaire, five functional scales, global health status, and nine symptom scales will be provided.

7.9.3 EORTC-QLQ-BN-20

Baseline measures of the transformed scales will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for 4 domains and 7 single items by cohort, based on participants with a baseline measurement.

Post-baseline measures and change from baseline of the transformed scales will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for 4 domains and 7 single items at each assessment time point by cohort. This analysis will be performed in participants who have an assessment at baseline and at least one on-study assessment.

EORTC-QLQ-BN-20 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., number of participants on treatment or in follow up), will be calculated along with reason for the questionnaire not completed and summarized for each assessment time point by cohort.

A by-participant listing containing all single items on the questionnaire, four functional domains, and seven single items will be provided.

[redacted]

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[10]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[11].

For death dates, the following conventions will be used for imputing partial dates:

If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.

- If the month or the year is missing, the death date will be imputed as the last known alive date.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known alive date.

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
- In case, the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions will be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

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

1 month = 30.4375 days and 1 year = 365.25 days

Duration (e.g. time from first diagnosis of RCC to first dosing date, duration response, and time to response) will be calculated as follows:

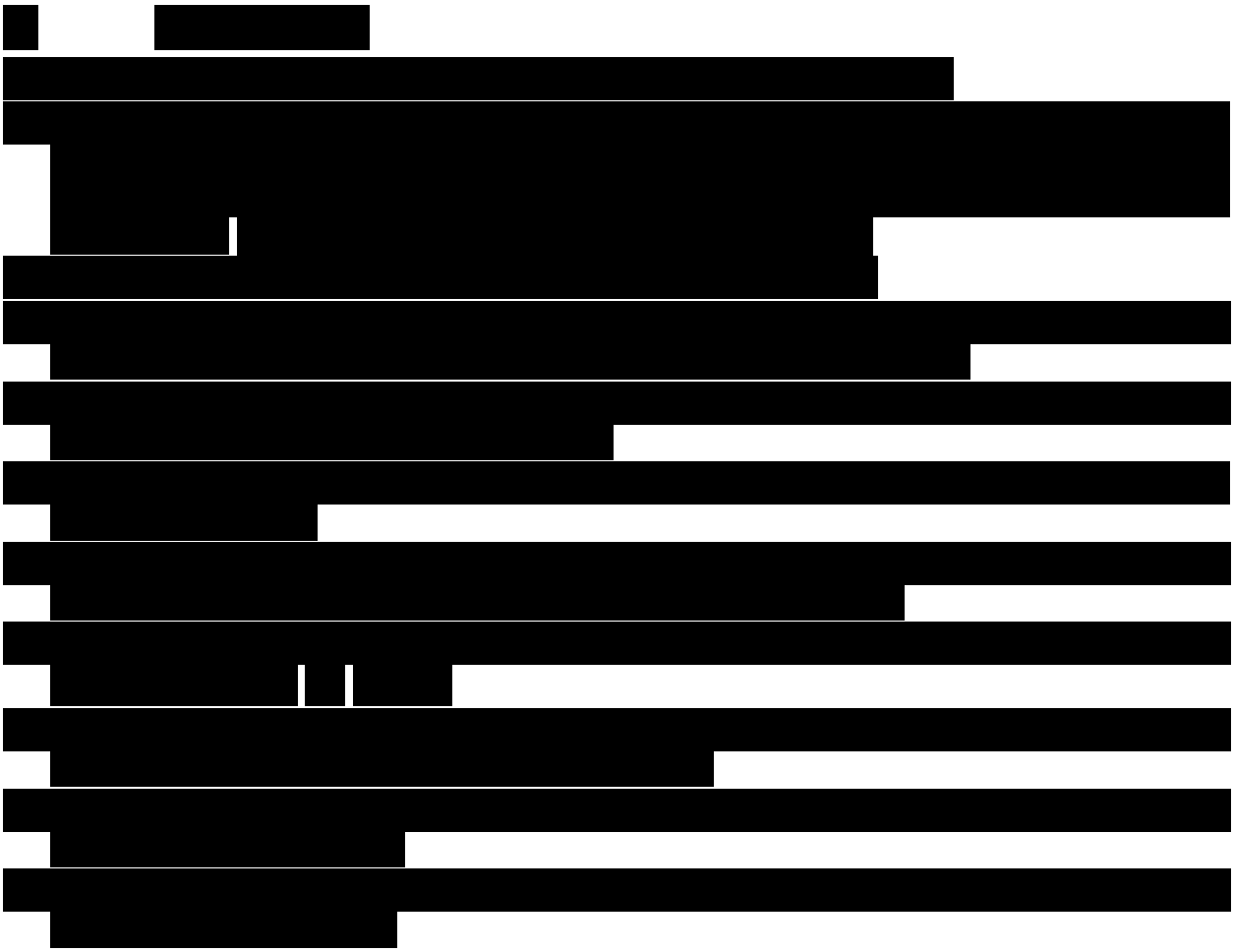
Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

Safety conventions from Programming may be summarized separately in an appendix.

9 CONTENT OF REPORTS

All analyses describe in this SAP will be included in the final Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings.



11 DOCUMENT HISTORY

Table 11-1: Document History

Version Number	Author(s)	Description
1.0		Initial version- 09 Feb 2018